IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ASTRAZENECA LP, ASTRAZENECA AB, ASTRAZENECA UK LIMITED, and ASTRAZENECA PHARMACEUTICALS LP, Plaintiffs, v. SIGMAPHARM LABORATORIES PHARMACEUTICAL INC., Defendant	Civil Action No. 15-1000-RGA CONSOLIDATED
ASTRAZENECA LP, ASTRAZENECA AB, ASTRAZENECA UK LIMITED, and ASTRAZENECA PHARMACEUTICALS LP, Plaintiffs, v. PRINSTON PHARMACEUTICAL INC., Defendant	Civil Action No. 15-1057-RGA

EXHIBITS A-L
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

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Dated: May 10, 2017

EXHIBIT A TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

REMARKS

Reconsideration of this application is requested. Claims 1-6, 14, 17 and 19-24 are in the case. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are captioned "**Version With Markings To Show Changes Made**."

I. THE REJECTIONS

Claim 14 stands rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite in light of the utility statement. In response, and without conceding to the merit of this rejection, reference to "prevention" has been deleted without prejudice. In addition, the language "of a platelet aggregation disorder" has been canceled without prejudice and replaced by "post-myocardial infarction". New claim 24 has also been presented which is directed to the treatment of stroke. Basis for claim14 as amended and new claim 24 appears in the originally filed specification at page 13, lines 22 and 23. No new matter is entered. Withdrawal of the rejection of claim 14 is now respectfully requested.

Claim 18 has been rejected as allegedly too long. In response, and again without conceding to the merit of this rejection, claim 18 has been canceled without prejudice, and replaced by new claims 19-23 which present the compounds of claim 18 in a series of separate claims. Withdrawal of this rejection is now respectfully requested.

Claim 1 stands rejected in light of the use of the word "solvate". This rejection is respectfully traversed.

A person of ordinary skill in this art would have no difficulty in understanding what is meant by "solvate" in the context of the presently claimed compounds. For example, as noted at page 13, line 12, the solvate may be water, ethanol, tetrahydrofuran or diethylether. Given this disclosure taken with the level or ordinary skill in this art, it is believed that no indefiniteness arises with respect to claim 1 in light of the use of the term "solvate". Reconsideration and withdrawal of this aspect of the formal rejection are accordingly respectfully requested.

II. U.S. Patent 6,251,910

The Action refers again to U.S. Patent 6,251,910. There is no clear statement in the Action as to the basis of rejection, if any, over this patent. The Examiner makes reference to "interference" and "an overlap problem" with regard to U.S. Patent 6,251,910. No such overlap is believed to exist. Moreover, U.S. Patent 6,251,910 and the present application Serial No. 09/508,195 are co-owned by the same assignee, namely AstraZeneca. Thus, the reference to interference is inapposite, since U.S. Patent 6,251,910 and the present application are commonly assigned.

As explained in the response of December 13, 2001, the claimed invention of the present application is an improvement over the disclosure of U.S. Patent 6,251,910. That response was accompanied by a Declaration executed by Anthony H. Ingell and Brian Springthorpe averring that of the nine compounds exemplified in the present

application, five were synthesized prior to the September 21, 1998 35 U.S.C. § 102(e) date of U.S. Patent 6,251,910. Utility of those compounds is demonstrated in the present specification at pages 13-16 and 42-43. U.S. Patent 6,251,910 is therefore not available as prior art under 35 U.S.C. § 102(e) against the presently claimed invention.

To further emphasize distinctions of the presently claimed invention over U.S. Patent 6,251,910, attached is a Declaration executed by Robert J. Riley (hereinafter the Riley Declaration), together with copies of references referred to in the Declaration. A PTO-1449 is also attached together with an IDS fee. The Examiner is requested to consider and initial the attached PTO-1449 and to return a copy of the initialed document to the undersigned with the next paper to issue in this application.

The Riley Declaration shows that the compounds exemplified in the present application exhibit an unexpected advantage of being active at a lower predicted dose in man as a result of a combination of increased metabolic stability together with high affinity for the P_{2T}-receptor (see paragraph 10 of the Declaration). In paragraphs 11 onwards of the Riley Declaration, data is provided establishing that exemplified compounds of the present application maintain P_{2T} potency and display unexpectedly higher metabolic stability to glucuronidation than the closest analogs of U.S. Patent 6,251,910.

In light of this evidence, it is clear that the presently claimed invention is patentably distinguished over the disclosure of U.S. Patent 6,251,910. Reconsideration and withdrawal of any outstanding rejections based on that patent are accordingly respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

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Leonard C. Mitchard
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

HARDERN et al

Serial No. **09/508,195**

Filed: **March 8, 2000**

For: **NOVEL COMPOUNDS**

Atty. Ref.: **3764-2**

Group: **1624**

Examiner: **Ford, J.**

* *

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

DECLARATION

Sir:

I, Robert J. Riley, do hereby declare and state as follows:

1) I have been employed by AstraZeneca UK Limited and its predecessor companies for ten years. I now work within the Department of Physical and Metabolic Sciences as a Principal Research Scientist, supervising thirteen laboratory workers. I received my undergraduate degree (BSc Hons) from the University of Liverpool in 1986 and my PhD from the University of Liverpool in 1989. My technical expertise is in the field of Drug Metabolism and Pharmacokinetics.

2) I am aware of both US patent number 6,251,910 (Guile *et al*) and US patent application number 09/508,195 (Hardern *et al*) that each disclose compounds which act as P_{2T}-receptor antagonists. These compounds may be used as pharmaceutical agents for inhibition of platelet aggregation. Both the patent (Guile *et al*) and the patent application (Hardern *et al*) have been assigned to AstraZeneca UK Limited. I am familiar with the compounds disclosed and I have been involved in testing and analyzing their biological activity.

3) The following factors are among those important in a compound having a low predicted dose in man:

   i) Good potency at the human receptor;

   ii) Good metabolic stability in man.

   Therefore increasing metabolic stability while maintaining affinity for the P_{2T}-receptor will result in effective treatment at a lower predicted human dose.

4) The compounds exemplified in Hardern *et al* are predicted to be active at a lower dose in man than those in Guile *et al* due to an unexpected combination of good potency at the P_{2T}-receptor and good human metabolic stability *in vitro*.

5) Good potency is defined as an affinity for the P_{2T}-receptor greater than 8 in the ligand binding assay described in the pharmacological data below.

6) It is well documented in the literature that *in vitro* measurements may be used to predict the *in vivo* metabolic stability of drugs. For example, this issue is discussed in the following papers:

   i) A D Rodrigues, Biochem. Pharmacol., 1994, 48, 2147

   ii) M Mistry, J B Houston, Drug Metab. Dispos.' 1987, 15, 710

   iii) J B Houston, Biochem. Pharmacol., 1994, 47, 1469

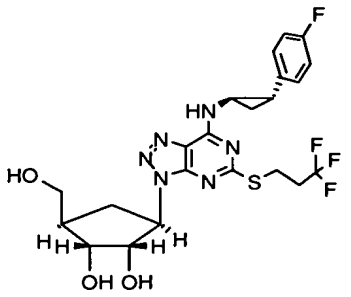
7) *In vitro* studies in human *hepatic* microsomes showed that compounds of the general structure exemplified in Guile *et al* are metabolised by oxidation and glucuronidation. The compounds exemplified in Hardern *et al* display the unexpected advantage of being more metabolically stable to both oxidation and glucuronidation. Since the compounds also maintain P_{2T}-receptor affinity the predicted therapeutic dose for inhibition of platelet aggregation in man shows advantage.

8) The rate of oxidation is measured by comparing the rate of oxidation of a test compound in human microsomes to a standard, dextromethorphan, a compound known to be rapidly metabolically cleared in man by oxidation (Martindale 23rd Edition, Pharmaceutical Press, 2002, p 1087). Therefore the higher the ratio the more metabolically stable the test compound.

9) The rate of glucuronidation is measured by comparing the rate of glucuronidation of a test compound in an *in vitro* glucuronosyltransferase assay to a standard, zileuton, a compound known to be rapidly metabolically cleared in man by glucuronidation (W M Awni etal. Clin. Pharmacokinet., 1995, 29 (suppl. 2) 49). Therefore the higher the ratio the more metabolically stable the test compound.

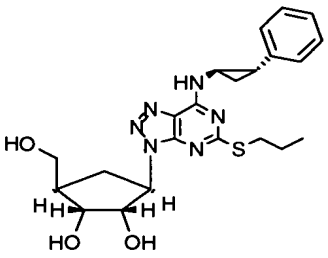
10) For the compounds exemplified in Hardern *et al* it can be shown that these compounds demonstrate the unexpected advantage of being active at a lower predicted dose in man as a result of a combination of increased metabolic stability together with high affinity for the P_{2T}-receptor.

11) The following compound is illustrated in Example 1 of Hardern *et al*:

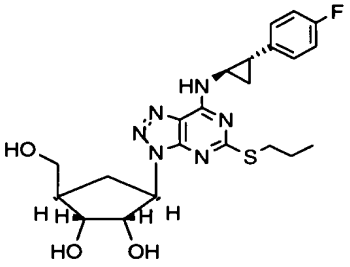


The following two compounds are exemplified in Guile *et* al:

Example 1



Example 61

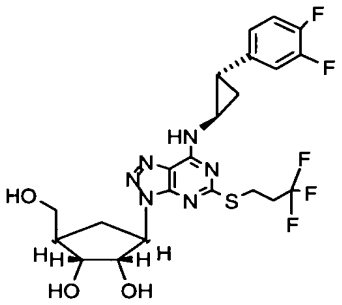


Of all the compounds exemplified in Guile *et al*, these two compounds are structurally closest to the compound exemplified in Hardern *et al* Example 1.

12) The data given in the table below shows that the Example 1 compound of Hardern *et al* maintains P_{2T} potency but displays unexpectedly higher metabolic stability to glucuronidation than the closest analogues in Guile *et al.*

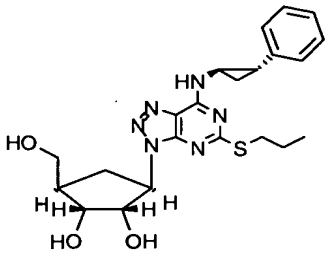
Example No	**US Patent or Application**	**P_{2T}-potency (Ki)**	**Human microsomes-stability to oxidation ratio to dex.**	**Human *in vitro* glucuronosyltransferase assay – stability to glucuronidation relative to zileuton**
Example 1	Hardern *et al*	8.4	Stable – no oxidation detected	27.8
Example 1	Guile *et al*	8.5	Stable	4.8
Example 61	Guile *et al*	8.3	>30	8.5

13) The following compound is illustrated in Example 2 of Hardern *et al*:

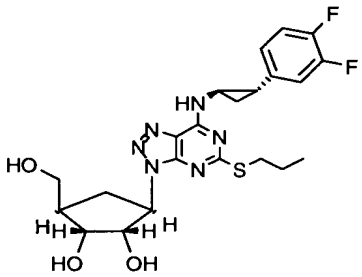


The following two compounds are the structurally closest examples in Guile *et al:*

Example 1



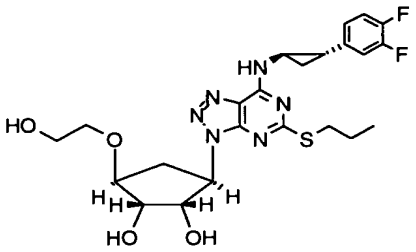
Example 69



14) The data given in the table below shows that the Example 2 compound of Hardern *et al* maintains P_{2T} potency but displays significantly higher metabolic stability to glucuronidation when compared to the closest analogues in Guile *et al.*

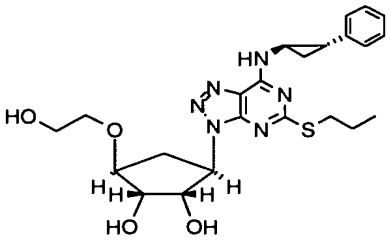
Example No	**US Patent or Application**	**P_{2T}-potency (Ki)**	**Human microsomes-stability to oxidation ratio to dex.**	**Human *in vitro* glucuronosyltransferase assay – stability to glucuronidation relative to zileuton**
Example 2	Hardern *et al*	8.3	Stable – no oxidation detected	Stable- no glucuronide detected
Example 1	Guile *et al*	8.5	Stable	4.8
Example 69	Guile *et al*	8.7	Stable	10.9

15) The following compound is illustrated in Example 3 of Hardern *et al*:

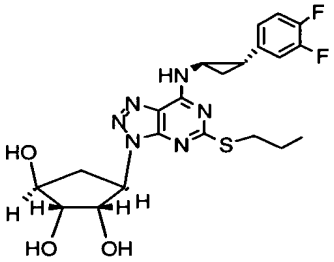


The following two compounds are the structurally closest examples in Guile *et al:*

Example 32



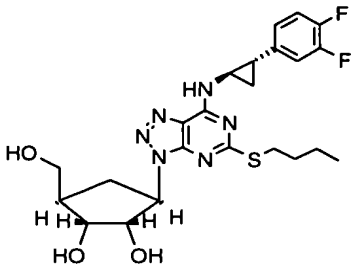
Example 68



16) The data given in the table below shows that the Example 3 compound of Hardern *et al* maintains P_{2T} potency but displays significantly higher metabolic stability to glucuronidation when compared to the closest analogues in Guile *et al*.

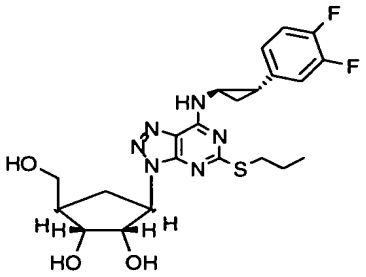
Example No	**US Patent or Application**	**P_{2T}-potency (Ki)**	**Human microsomes - stability to oxidation ratio to dex.**	**Human *in vitro* glucuronosyltransferase assay – stability to glucuronidation relative to zileuton**
Example 3	Hardern *et al*	8.7	24	Stable- no glucuronide detected
Example 32	Guile *et al*	8.3	13	24
Example 68	Guile *et al*	8.6	stable	3.9

17) The following compound is illustrated in Example 4 of Hardern *et al*:



The following compound is the structurally closest example in Guile *et al*:

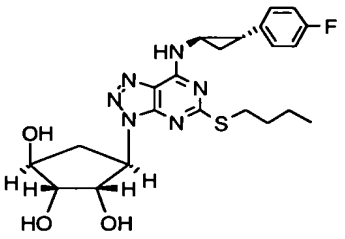
Example 69



18) The data given in the table below shows that the Example 4 compound of Hardern *et al* maintains P_{2T} potency but displays significantly higher metabolic stability to glucuronidation when compared to the closest analogue in Guile *et al*.

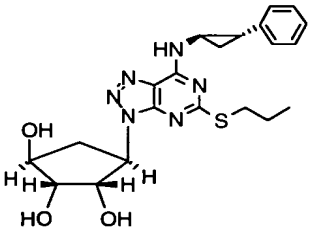
Example No	**US Patent or Application**	**P_{2T}- potency (Ki)**	**Human microsomes - stability to oxidation ratio to dex.**	**Human *in vitro* glucuronosyltransferase assay – stability to glucuronidation relative to zileuton**
Example 4	Hardern *et al*	8.3	29	42.8
Example 69	Guile *et al*	8.7	Stable	10.9

19) The following compound is illustrated in Example 5 of Hardern *et al*:

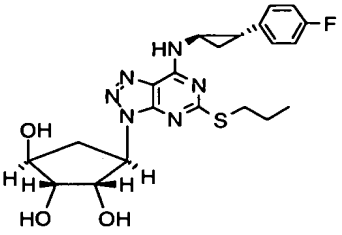


The following two compounds are the structurally closest examples in Guile *et al:*

Example 12



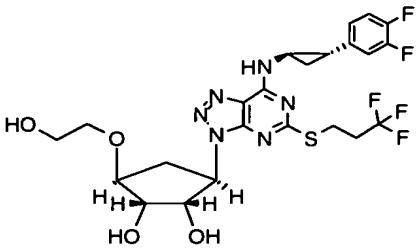
Example 19

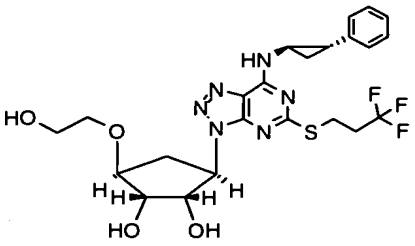


20) The data given in the table below shows that the Example 5 compound of Hardern *et al* maintains P_{2T} potency but displays significantly higher metabolic stability to glucuronidation when compared to the closest analogues in Guile *et al*.

Example No	**US Patent or Application**	**P_{2T}-potency (Ki)**	**Human microsomes - stability to oxidation ratio to dex.**	**Human *in vitro* glucuronosyltransferase assay – stability to glucuronidation relative to zileuton**
Example 5	Hardern *et al*	8.4	>30	Stable – no glucuronide detected
Example 12	Guile *et al*	8.6	Stable	2.7
Example 19	Guile *et al*	8.6	10.3	7.6

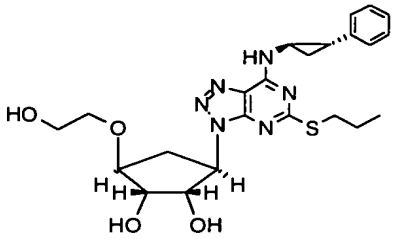
21) The following compounds are illustrated in Examples 6 and 7 of Hardern *et al*:



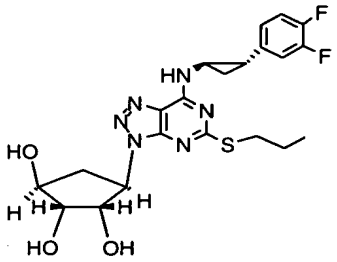


The following two compounds are the structurally closest examples in Guile *et al:*

Example 32



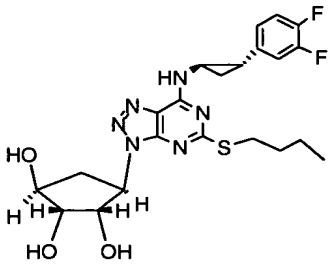
Example 68



22) The data given in the table below shows that the Example 6 compound and the Example 7 compound of Hardern *et al* maintain P_{2T} potency but display significantly higher metabolic stability to glucuronidation when compared to the closest analogues in Guile *et al.*

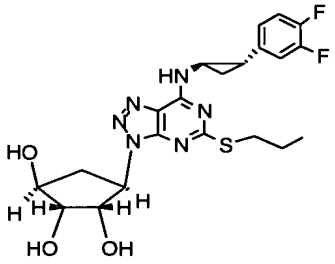
Example No	**US Patent or Application**	**P_{2T}- potency (Ki)**	**Human microsomes - stability to oxidation ratio to dex.**	**Human *in vitro* glucuronosyltransferase assay – stability to glucuronidation relative to zileuton**
Example 6	Hardern *et al*	9.0	31.8	Stable – no glucuronide detected
Example 7	Hardern *et al*	8.7	>24	50
Example 32	Guile *et al*	8.3	13	23.8
Example 68	Guile *et al*	8.6	stable	3.9

23) The following compound is illustrated in Example 8 of Hardern *et al*:

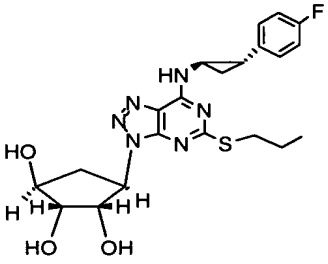


The following three compounds are the structurally closest examples in Guile *et al:*

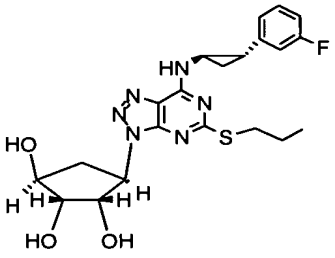
Example 68



Example 19



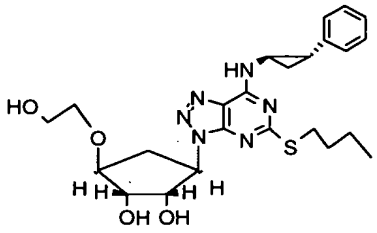
Example 99



24) The data given in the table below shows that the Example 8 compound of Hardern *et al* maintains P_{2T} potency but displays significantly higher metabolic stability to glucuronidation when compared to the closest analogues in Guile *et al*.

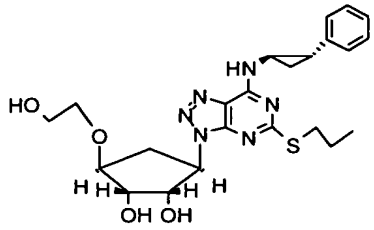
Example No	**US Patent or Application**	**P_{2T}-potency (Ki)**	**Human microsomes - stability to oxidation ratio to dex.**	**Human *in vitro* glucuronosyltransferase assay – stability to glucuronidation relative to zileuton**
Example 8	Hardern *et al*	8.4	>25	>20
Example 68	Guile *et al*	8.6	stable	3.9
Example 19	Guile *et al*	8.6	10.3	7.6
Example 99	Guile *et al*	8.8	stable	3.5

25) The following compound is illustrated in Example 9 of Hardern *et al*:



The following compound is the structurally closest example in Guile *et al:*

Example 32



26) The data given in the table below shows that the Example 9 compound of Hardern *et al* maintains P_{2T} potency but displays significantly higher metabolic stability to oxidation when compared to the closest analogues in Guile *et al.*

Example No	**US Patent or Application**	**P_{2T}- potency (Ki)**	**Human microsomes - stability to oxidation ratio to dex.**	**Human *in vitro* glucuronosyltransferase assay – stability to glucuronidation relative to zileuton**
Example 9	Hardern *et al*	8.5	>25	26
Example 32	Guile *et al*	8.3	13	23.8

I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Robert J Riley

31st July, 2002
Date

EXHIBIT B TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 17 (2007) 6013–6018

From ATP to AZD6140: The discovery of an orally active reversible $P2Y_{12}$ receptor antagonist for the prevention of thrombosis

Brian Springthorpe,* Andrew Bailey, Patrick Barton, Timothy N. Birkinshaw, Roger V. Bonnert, Roger C. Brown, David Chapman, John Dixon, Simon D. Guile, Robert G. Humphries, Simon F. Hunt, Francis Ince, Anthony H. Ingall, Ian P. Kirk, Paul D. Leeson, Paul Leff, Richard J. Lewis, Barrie P. Martin, Dermot F. McGinnity, Michael P. Mortimore,† Stuart W. Paine, Garry Pairaudeau, Anil Patel, Aaron J. Rigby, Robert J. Riley, Barry J. Teobald, Wendy Tomlinson, Peter J. H. Webborn and Paul A. Willis

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Abstract—Starting from adenosine triphosphate (ATP), the identification of a novel series of $P2Y_{12}$ receptor antagonists and exploitation of their SAR is described. Modifications of the acidic side chain and the purine core and investigation of hydrophobic substituents led to a series of neutral molecules. The leading compound, **17** (AZD6140), is currently in a large phase III clinical trial for the treatment of acute coronary syndromes and prevention of thromboembolic clinical sequelae.

Platelet aggregation, superimposed on plaque rupture, is a critical mechanism involved in transforming otherwise clinically stable atherosclerotic disease into an acute, potentially life-threatening arterial thrombotic event, such as unstable angina, myocardial infarction or thrombotic stroke. Platelets adhere to the ruptured arterial plaque and aggregate in response to a variety of local and systemic stimuli, including mediators such as adenosine diphosphate (ADP), adrenaline, thrombin and 5-hydroxytryptamine. Whatever the stimulation, the final common steps are exposure of the GPIIb/IIIa receptor complex and subsequent cross-linking of the platelets by fibrinogen.[1] The platelet aggregate is further consolidated by formation of fibrin, resulting in a firm, adherent clot.

ADP has a pivotal role in this process since the stimuli exert much of their effect by release of ADP from storage granules into the medium. The consequences of this are that the $P2Y_{12}$ receptor (formerly known as the P_{2T} receptor) on the platelet is stimulated, shape change occurs and the GPIIb/IIIa complex is exposed. Nearby platelets are also activated and the initial pro-aggregatory signal is amplified. Therefore, the ADP/$P2Y_{12}$ pathway plays a key amplifying role in the overall platelet response. Against this background, it is clear that inhibiting the effect of ADP on the $P2Y_{12}$ receptor significantly inhibits platelet aggregation and thereby prevents the formation of a firm, cross-linked thrombus.[2] The discovery and clinical use of the irreversible $P2Y_{12}$ antagonist clopidogrel[3] (Fig. 1) has confirmed the clinical impact of inhibiting this target. Although this anti-platelet agent has improved the management of acute and sub-acute coronary artery disease, several features of this agent leave room for improvement, such that more effective treatments are predicted to further improve clinical outcomes.

Using ATP, the natural antagonist ($pIC_{50} = 3.5$) of the $P2Y_{12}$ receptor, as a chemical starting point, we discovered **1** (AR-C69931MX, cangrelor, Fig. 1)[4] as a potent

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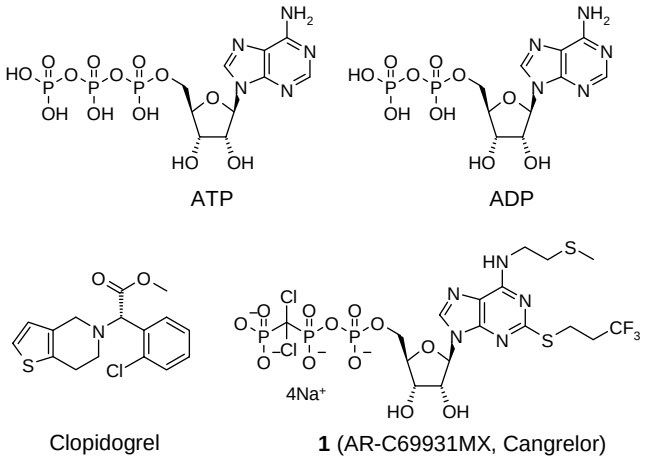


Figure 1. Structures of ATP, ADP, clopidogrel and cangrelor.

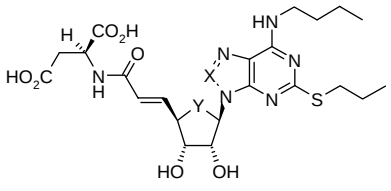
and selective $P2Y_{12}$ receptor antagonist suitable for intravenous use only. Compound **1** is currently in phase III clinical trials as an ultra-short acting, intravenously administered, antithrombotic agent.

This letter describes how the physical and chemical properties of **1** were modified in order to find potent, selective and orally active $P2Y_{12}$ antagonists.

Since ATP, the endogenous antagonist of the $P2Y_{12}$ receptor, differs from the agonist ADP in having a γ-phosphate group, we hypothesized that this terminal acidic group was essential for antagonism. Efforts were therefore directed towards finding alternative acidic groups which could mimic the polyphosphate chain and particularly the γ-phosphate unit of ATP. This initial strategy led to the discovery of an aspartic acid-derived dicarboxylate **2** (Table 1), which was ~300-fold less potent ($pIC_{50} = 7.0$) than the triphosphate **1** ($pIC_{50} = 9.4$).

Further extensive variation of the substituents on the adenosine core of **2** did not lead to improved potency and it was decided to make more fundamental changes to the core structure.

Table 1. $P2Y_{12}$ antagonist potency of aspartic acid derivatives (**2**–**4**)



Compound	X	Y	$hP2Y_{12}$ pIC_{50}[a]
2	C	O	7.0
3	N	O	9.5
4	N	CH_2	9.3

[a] ADP-induced aggregation assay using washed platelets as described in Ref. 7.

The triazolopyrimidine heterocycle has been identified as an isostere of purine and has been successfully employed in the anticancer and antiviral areas.[5] Utilising this heterocycle led to **3** in which the $P2Y_{12}$ potency had unexpectedly increased ($pIC_{50} = 9.5$). This change resulted in the identification of the first potent and selective non-phosphate $P2Y_{12}$ antagonist **3** having activity equivalent to that of triphosphate **1**.

In response to the potential instability of the glycosidic bond to enzymatic cleavage we investigated replacing the ribose sugar with a cyclopentyl unit, a structural change that has been successful in a number of areas, including the antiviral field.[6] In compound **4** we have retained the potencies of **1** and **3** but have now successfully moved away from a classic purinergic core structure.

While these changes provided improved potency over compound **2**, compounds **3** and **4** were cleared rapidly in the rat by the biliary route. The properties of these molecules are not favourable for oral absorption: doubly negatively charged, molecular weight >500, >5 H-bond donors. Variation of the substituents on the triazolopyrimidine core of structure **4** did not improve potency nor, more importantly, metabolic properties, so attention was turned once more to the acidic side chain, with the goal of reducing its complexity.

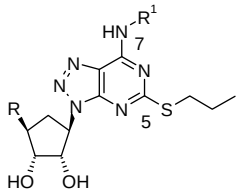
The parallel chemistry approach employed required an assay able to tolerate higher concentrations of DMSO and with higher throughput than the traditional ADP-induced aggregation in washed platelets.[7] A radiolabelled displacement binding assay was developed[8] to support this increased throughput and all subsequent data were generated using this binding assay. The switch from the functional to binding assay was validated with earlier, suitably soluble compounds, which demonstrated similar potency in both systems.

An example of the stepwise truncation from compound **4** is the monocarboxylic acid **5**, which was surprisingly potent ($pK_i = 8.3$), a result at odds with the γ-phosphate theory. Unfortunately, compound **5** was still cleared by the biliary route and had low bioavailability. However, more surprising and of crucial importance was the observation that the neutral molecules **6** and **7** (Table 2) had modest but significant $P2Y_{12}$ affinity.

Significantly, these neutral molecules were cleared in the rat solely by metabolic processes, which we felt able to understand and manipulate. While the affinity of **6** and **7** was reduced compared with compound **5**, these molecules were more amenable to rapid parallel synthesis at the 5- and 7-positions as a means of improving affinity (Schemes 1 and 2: synthesis of the intermediates according to our published procedures).[9] In all, some 6000 analogues were synthesised.

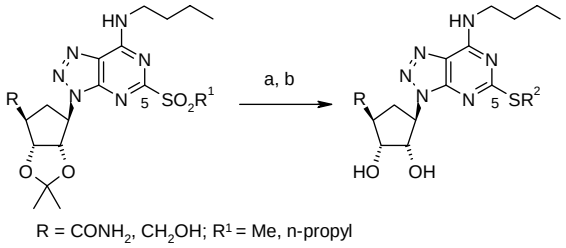
Position 5 was varied by displacement of a sulfone-leaving group by S, O and N nucleophiles. It was found that polar substituents were not well tolerated and sulfur linked groups were consistently more potent than their oxygen and nitrogen analogues. From the results it

Table 2. $P2Y_{12}$ affinity and rat pharmacokinetics of compounds with simplified C4′ side chains (**5**–**10**)

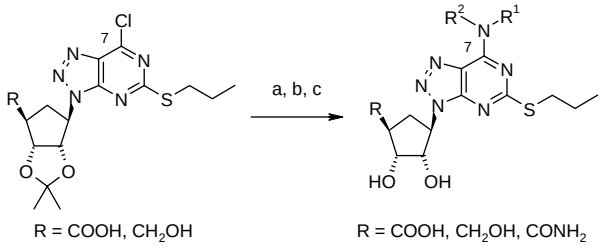


Compound	R	R^1	hP2Y$_{12}$ pK_i[a]	Rat Clp[b]	Rat V_{ss}[b]	Rat $T_{1/2}$[b]	Rat F%[c]
5	COOH	Butyl	8.3	30	0.4	0.5	<5
6	$CONH_2$	Butyl	7.7	21	1.6	1.4	<5
7	CH_2OH	Butyl	7.1	29	2.3	1.2	<5
8	COOH		9.6	16	0.5	0.5	
9	$CONH_2$		8.8	20	2.2	2.0	<5
10	CH_2OH		8.3	16	2.9	2.5	35

Units: Clp, mL/min/kg; V_{ss}, L/kg; $T_{1/2}$, h; F, bioavailability.
[a] Assay described in Ref. 8.
[b] Dosed at ~3 mg/kg (iv).
[c] Dosed at 3–10 mg/kg (po).



Scheme 1. Reagents and conditions: (a) $NaSR^2$, DMF, 20 °C, 1 h; (b) TFA–H_2O (9:1), 20 °C, 2 h.



Scheme 2. Reagents and conditions: (a) R^1R^2NH, *N*,*N*-diisopropylethylamine, CH_2Cl_2, 20 °C, 16 h; (b) R = (COOH → $CONH_2$), oxalyl chloride, CH_2Cl_2, 20 °C, 2 h, 35% aq ammonium hydroxide, CH_2Cl_2, 20 °C, 2 h; (c) TFA–H_2O (9:1), 20 °C, 2 h.

was concluded that *S*-propyl substitution at position 5 was optimal.

Investigation of substitution at the 7-position was accomplished by displacement of chloride by amines. Using amines bearing polar substituents, or secondary amines, led to reduced affinity. In only one case was affinity significantly increased over that of the butyl substituent, but the enhancement found with racemic *trans*-2-phenylcyclopropylamine was crucial for achieving our objectives of potency and good preclinical metabolic properties.

Separation[10] of the enantiomers of *trans*-phenylcyclopropylamine showed that the 1*R*,2*S* isomer was more potent than the 1*S*,2*R* isomer.

Not only did this discovery lead to a >10-fold increase in affinity (**5** vs **8**, **6** vs **9** and **7** vs **10**), but the alcohol derivative **10** showed significant oral bioavailability in the rat (Table 2) and a sustained inhibition of ADP-induced platelet aggregation ex vivo in the dog following oral administration.

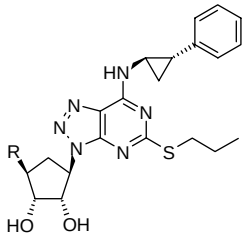
While the alcohol **10** had acceptable $P2Y_{12}$ affinity and good preclinical pharmacokinetics in both the rat and the dog, investigation of the metabolism of the compound in hepatocytes demonstrated marked species differences in biotransformation profiles.[11] Whereas oxidation was the predominant route of metabolism in rat hepatocytes, glucuronidation at the C4′ side chain hydroxyl group was the major biotransformation pathway in hepatocytes from dogs and humans.

This observation led us to set up a primary assay for glucuronidation using UDPGA supplemented rat, dog and human microsomes, in addition to the traditional NADPH supplemented microsomal assays used to measure oxidation.[11,12] These assays were applied in parallel to aid compound selection for final evaluation in human hepatocytes. Relative figures for resistance to glucuronidation and oxidation were determined by the inclusion in the assay of known standards: zileuton for the glucuronidation assay and dextromethorphan for the oxidation assay, the aim being to identify compounds with ratios of >20 × zileuton and >10 × dextromethorphan. In vitro–in vivo modelling had suggested that compounds showing such figures could be expected to have a metabolic clearance via glucuronidation and oxidation equivalent to <10% hepatic extraction (<2 mL/min/kg).

The hydroxymethyl compound **10**, although having good bioavailability, did not reach our desired criterion for resistance to glucuronidation. Further neutral alcohols were examined (Table 3) and the hydroxyethoxy **11** and hydroxyethyl **13** analogues achieved the desired metabolic stability ratios while retaining good bioavailability.

Of particular note is compound **14** (Table 3, R = H) which has a pK_i of 8.6. This is surprising since all functionality has been removed from this position and yet affinity is only 1/10 that of the triphosphate **1**. We propose that while in the triphosphate series activity is dominated by the electrostatic interactions of the acid side chain, new receptor-binding interactions have been introduced utilising the triazolopyrimidine and the lipophilic phenylcyclopropyl group. Compound **14** is, however, unstable to glucuronidation and overall the

Table 3. $P2Y_{12}$ antagonist affinity, metabolic stability and bioavailability of C4′ side chain alcohols



Compound	R	hP2Y$_{12}$ pK_i	UDPGA ratio[a]	NADPH ratio[b]	Rat F%
10	CH_2OH	8.3	5	>30	35
11	$O(CH_2)_2OH$	8.5	24	13	26
12	OH	8.7	3	Stable	50
13	$(CH_2)OH$	8.2	19	27	37
14	H	8.6	1	NT	38

Stable, turnover below limit of quantification; NT, not tested.
[a] UDPGA assay: required ratio to zileuton >20.
[b] NADPH assay: required ratio to dextromethorphan >10.

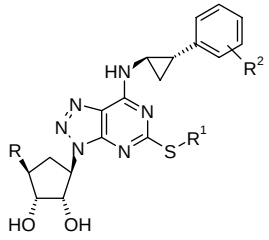
data in Table 3 show the hydroxyl side chain has an important effect on metabolic stability but little effect on affinity.

Finally, further optimisation by fine-tuning the substitution of the phenyl ring and 5-*S*-propyl substituent of **10** and **11** provided compounds **15**–**18** (Table 4) with acceptable affinity and metabolic stability suitable for further progression.

Preclinical pharmacokinetic data for 3,4-difluorophenyl compounds **16**–**18** are shown in Table 5.

Table 4. Optimising metabolic stability by substitution of the phenylcyclopropyl group

15,16: R = CH_2OH
17,18: R = $O(CH_2)_2OH$



Compound	R^1	R^2	hP2Y$_{12}$ pK_i	UDPGA ratio[a]	NADPH ratio[b]
15	$(CH_2)_2CF_3$	H	8.3	19	Stable
16	$(CH_2)_2CF_3$	3,4-DiF	8.3	Stable	>30
17	$(CH_2)_2CH_3$	3,4-DiF	8.7	Stable	24
18	$(CH_2)_2CF_3$	3,4-DiF	9.2	Stable	32

Stable, turnover below limit of quantification.
[a] UDPGA assay: required ratio to zileuton >20.
[b] NADPH assay: required ratio to dextromethorphan >10.

Table 5. Rat and dog pharmacokinetics for compounds **16**–**18**

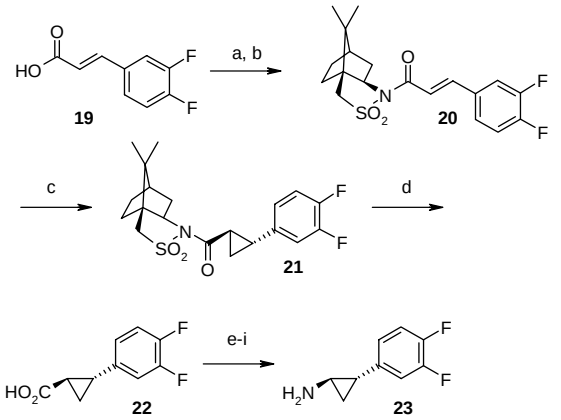
	Rat Clp[a]	Rat V_{ss}[a]	Rat $T_{1/2}$[a]	Rat F%[b]	Dog Clp[a]	Dog V_{ss}[a]	Dog $T_{1/2}$[a]	Dog F%[b]
16	11	2.7	3.0	17	16.5	5.6	4.8	59
17	21	3.8	2.6	24	9.0	3.0	2.9	72
18	12	2.1	2.5	9	NT	NT	NT	NT

Units: Clp, mL/min/kg; V_{ss}, L/kg; $T_{1/2}$, h; F, bioavailability; NT, not tested.
[a] Dosed at ~3 mg/kg (iv) in rat and 1 mg/kg (iv) in dog.
[b] Dosed at 3–10 mg/kg (po) in rat and 1 mg/kg (po) in dog.

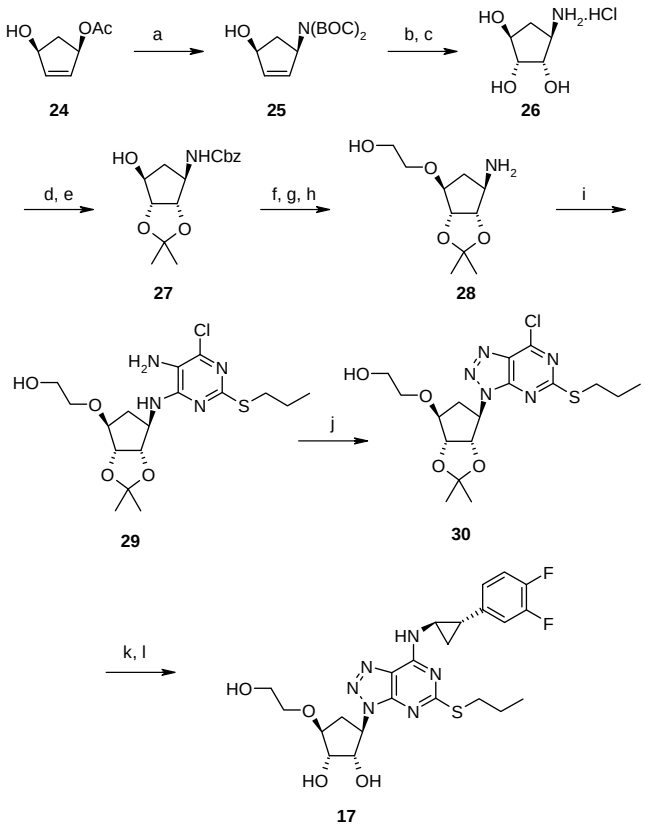
Compound **17** (AZD6140) was chosen over **16** and **18** for progression into human testing on the basis of a lower predicted dose (driven by a combination of potency and pharmacokinetic properties in pre-clinical species).

AZD6140 can be synthesised using the route outlined in Schemes 3a and 3b. Synthesis of the (1*R*,2*S*)-*trans* phenylcyclopropylamine begins with derivatisation of substituted cinnamic acid **19** with Oppolzer's sultam[13] to give **20**. Diastereoselective cyclopropanation[14] then provides, after recrystallisation, cyclopropylamide **21** in high chiral purity which is readily saponified to acid **22**. A four-step Curtius rearrangement[15] gives the cyclopropylamine **23**, which is conveniently isolated as a tartrate salt.

Synthesis of the core utilises commercially available acetate **24** which is cleanly converted to the protected amine **25** under palladium catalysis.[16] Osmium catalysed *cis* dihydroxylation[17] occurs with good diastereoselectivity to give, following amine deprotection, the aminotriol **26**. Reprotection of the amine as a benzyl carbamate and protection of the diol as an acetonide gives alcohol **27** suitable for alkylation. The hydroxyethyl side chain is next incorporated by reaction with ethyl bromoacetate followed by reduction to give key intermediate **28**. Reaction of **28** with 4,6-dichloro-2-propylthio-pyrimidine-5-amine[9] gives **29** which is converted to the triazolopyrimidine **30** under diazotization conditions. Finally,



Scheme 3a. Reagents and conditions: (a) $SOCl_2$; (b) sultam salt (80%; two steps); (c) CH_2N_2, $Pd(OAc)_2$ then recrystallise from EtOH (50%); (d) LiOH, H_2O, THF, 50 °C (99%); (e) $ClCO_2Et$, TEA, acetone, H_2O; (f) NaN_3, H_2O; (g) toluene, reflux; (h) 6 M HCl, reflux; (i) L-tartaric acid, EtOH (62%, five steps).



Scheme 3b. Reagents and conditions: (a) $(BOC)_2NNa$, $Pd(PPh_3)_4$, THF (92%); (b) OsO_4, NMO, THF, H_2O (100%); (c) HCl, MeOH, H_2O (96%); (d) dimethoxypropane, pTSA, acetone (86%); (e) CbzCl, DIPEA, MIBK (95%); (f) Bu^tOK, ethyl bromoacetate, THF; (g) $LiBH_4$, THF (86%; two steps); (h) H_2, Pd/C, EtOH (99%); (i) 4,6-dichloro-2-propylthio-pyrimidine-5-amine, DIPEA, DMF (75%); (j) isoamylnitrite, CH_3CN (88%); (k) **23**, DIPEA, DCM (99%); (l) TFA, H_2O (90%).

chloro displacement with amine **23** followed by deprotection gives **17**.

Phase I and phase II studies have confirmed the predicted pharmacokinetic and pharmacodynamic profile of the compound and a double blind comparison with clopidogrel, on a background of low-dose aspirin, has shown **17** to have superior anti-platelet activity as measured ex vivo by light transmission aggregometry.[18]

In summary, beginning with ATP, a poor lead for an oral programme, we have discovered oral $P2Y_{12}$ antagonists with clinical potential. Key elements in the medicinal chemical journey from ATP to **1** to **17** were:

(a) introducing affinity-enhancing 5,7-hydrophobic substituents;
(b) replacement of the labile triphosphate group;
(c) changing the core purine to a triazolopyrimidine, increasing affinity >100-fold;
(d) finding the first nonacidic reversible antagonists (e.g., **6** and **7**);
(e) introducing the *trans*-2-phenylcyclopropylamino substituent, increasing affinity >10-fold; and
(f) identifying metabolically stable neutral compounds by modifying the hydrophobic phenylcyclopropyl group and the hydroxylic side chain substituent.

In making these changes, the structure–activity relationships moved away from dependency on the acidic side chain, allowing identification of potent and orally bioavailable non-nucleotide reversible $P2Y_{12}$ antagonists. Compound **17** has now progressed to phase III clinical trials in acute coronary syndromes.

Acknowledgments

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Supplementary data

Experimental details for the General Schemes 1 and 2 and supporting analytical data (NMR, MS and elemental analyses) for compounds **2**–**18** can be found in the online version. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2007.07.057.

References and notes

1. Frishman, W. H.; Burns, B.; Atac, B.; Alturak, N.; Altajar, B.; Lerrick, K. *Am. Heart J.* **1995**, *130*, 877.
2. Leff, P.; Robertson, M. J.; Humphries, R. G. In *Purinergic Approaches in Experimental Therapeutics*; Jacobson, K. A., Jarvis, M. J., Eds.; Wiley-Liss: New York, 1997; pp 203–216.
3. (a) CAPRIE Steering Committee (CAPRIE). *Lancet* **1996**, *348*, 1329; (b) The Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators (CURE). *N. Engl. J. Med.* **2001**, *345*, 494.
4. (a) Ingall, A. H.; Dixon, J.; Bailey, A.; Coombs, M. E.; Cox, D.; McInally, J. I.; Hunt, S. F.; Kindon, N. D.; Teobald, B. J.; Willis, P. A.; Humphries, R. G.; Leff, P.; Clegg, J. A.; Smith, J. A.; Tomlinson, W. *J. Med. Chem.* **1999**, *42*, 213; (b) Humphries, R. G. *Haematologica* **2000**, *85*, 66.
5. Albert, A.. In *Advances in Heterocyclic Chemistry*; Katritzky, A. R., Ed.; Academic Press, 1986; 39, pp 117–180.
6. Marquez, V. E.; Lim, M. L. *Med. Res. Rev.* **1986**, *6*, 1.
7. Aggregation of human washed platelets was assessed turbidimetrically in 96-well plates as a decrease in absorbance (650 nm). The washed platelets were incubated with the test compounds for 5 min before addition of 30 μM ADP. Antagonist potency was estimated as a % inhibition of the control ADP response to obtain a pIC_{50}. Full assay details are given in: Humphries, R. G.; Tomlinson, W.; Ingall, A. H.; Cage, P. A.; Leff, P. *Br. J. Pharmacol.* **1994**, *113*, 1057.
8. Binding data were obtained in washed platelets in 96-well plates, each well containing [^{125}I] radiolabelled $P2Y_{12}$ antagonist, test compounds and washed platelets. After 30 min incubation, the reaction was terminated by filtration, washing of the platelets and the bound radioactivity was measured and used to derive a pK_i. Full assay details

are given in: Kirk, I. PCT Int. Appl. WO200033080, 2000; *Chem. Abstr.* 2000, *133*, 14307.
9. (a) Bonnert, R. V.; Ingall, A. H.; Springthorpe, B.; Willis, P. A. PCT Int. Appl. W0199828300, 1998; *Chem, Abstr*. **1998**, *129*, 95506; (b) Guile, S. D.; Ingall, A. H.; Springthorpe, B.; Willis, P. A. PCT Int. Appl. WO199905143, 1999; *Chem, Abstr*. **1999**, *130*, 168386.
10. Mitscher, L. A.; Sharma, P. N.; Chu, D. T. W.; Shen, L. L.; Pernet, A. G. *J. Med. Chem.* **1986**, *29*, 2044.
11. Martin, I. J.; Lewis, R. J.; Bernstein, M. A.; Beattie, I. G.; Martin, C. A.; Riley, R. J.; Springthorpe, B. *Drug Metab. Dispos.* **2006**, *34*, 1502.
12. Bouska, J. J.; Bell, R. L.; Goodfellow, C. L.; Stewart, A. O.; Brooks, C. D.; Carter, G. W. *Drug Metab. Dispos.* **1997**, *25*, 1032.
13. For review, see Oppolzer, W. *Pure Appl. Chem.* **1990**, *62*, 1241.
14. Vallgarda, J.; Hacksell, U. *Tetrahedron Lett.* **1991**, *32*, 5625.
15. Shiori, T. In *Comprehensive Organic Synthesis, Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Trost, M. T., Fleming, I., Winterfeldt, E., Eds., 1st ed.; Pergamon Press: London, 1991; pp 795–827.
16. Jumnah, R.; Williams, J. M. J.; Williams, A. C. *Tetrahedron Lett.* **1993**, *34*, 6619.
17. See Trost, B. M.; Kuo, G.-H.; Benneche, T. *J. Am. Chem. Soc.* **1988**, *110*, 621, and references cited therein.
18. Husted, S.; Emanuelsson, H.; Heptinstall, S.; Sandset, P. M.; Wickens, M.; Peters, G. *Eur. Heart J.* **2006**, *27*, 1038.

EXHIBIT C TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

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DRUG METABOLISM AND DISPOSITION
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Absorption, Distribution, Metabolism, and Excretion of Ticagrelor in Healthy Subjects

Renli Teng, Stuart Oliver, Martin A. Hayes, and Kathleen Butler

AstraZeneca LP, Wilmington, Delaware (R.T., K.B.); AstraZeneca LP, Alderley Park, Macclesfield, Cheshire, United Kingdom (S.O.); and AstraZeneca R&D Mölndal, Mölndal, Sweden (M.A.H.)

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ABSTRACT:

Ticagrelor [(1*S*,2*S*,3*R*,5*S*)-3-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol)] is a reversibly binding oral $P2Y_{12}$ receptor antagonist in development for the prevention of thrombotic events in patients with acute coronary syndromes. The pharmacokinetics, metabolism, and excretion of ticagrelor were investigated over 168 h in six healthy male subjects receiving a single oral suspension dose of 200 mg of [^{14}C]ticagrelor. Ticagrelor was rapidly absorbed with a maximum plasma concentration at 1.5 h. The major active metabolite, AR-C124910XX, is formed by *O*-deethylation. Exposure to AR-C124910XX was 29% of peak and 40% of overall exposure to ticagrelor. In most subjects, radioactivity was undetectable in plasma after 20 h and whole blood after 12 h (half-life values of 6.3 and 4.6 h, respectively). The ratio of radioactivity in plasma to whole blood was 1.69, suggesting that ticagrelor and its metabolites are largely restricted to the plasma space. Mean radioactivity recovery was 26.5% in urine and 57.8% in feces. Major circulating components in the plasma and feces were identified as ticagrelor and AR-C124910XX, whereas in urine the major components were metabolite M5 (AR-C133913XX) and its glucuronide conjugate M4. Levels of unchanged ticagrelor and AR-C124910XX were <0.05% in the urine, indicating that renal clearance of ticagrelor and AR-C124910XX is of minor importance. Interindividual variability was small in both urine and fecal extracts with only small quantitative differences. All 10 of the metabolites were fully or partially characterized and a full biotransformation pathway was proposed for ticagrelor, in which oxidative loss of the hydroxyethyl side chain from ticagrelor forms AR-C124910XX and a second oxidative pathway leads to *N*-dealkylation of ticagrelor, forming AR-C133913XX.

Introduction

Standard therapy to reduce the risk of thrombotic complications in patients with acute coronary syndromes is currently aspirin in combination with clopidogrel (Yusuf et al., 2001; Bassand et al., 2007). However, there is still a need for treatment regimens with improved efficacy. New therapies with more optimal and consistent inhibition of platelet aggregation are in development to address this need.

Ticagrelor [(1*S*,2*S*,3*R*,5*S*)-3-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl) cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol; AZD6140] is a reversibly binding, noncompetitive, orally administered $P2Y_{12}$ receptor antagonist that is in clinical development for reduction of clinical thrombotic events in patients with acute coronary syndromes (van Giezen and Humphries 2005; Springthorpe et al., 2007; James et al., 2009). It is one of a chemical class of antiplatelet agents termed the cyclopentyltriazolopyrimidines, which act directly on the $P2Y_{12}$ receptor without requiring metabolic activation. In comparative trials, ticagrelor has produced greater and more consistent levels of inhibition of platelet aggregation and has a favorable trend in reducing risk for myocardial infarction compared with clopidogrel, without increasing the risk of major bleeding (Husted et al., 2006; Cannon et al., 2007; Storey et al., 2007). In the phase III PLATelet inhibition and patients Outcomes (PLATO) trial, treatment with ticagrelor versus clopidogrel significantly reduced the rate of death from vascular causes, myocardial infarction, or stroke [9.8 versus 11.7% (hazard ratio, 0.84; 95% CI, 0.77–0.92; $P < 0.001$)] (Wallentin et al., 2009).

Ticagrelor has one active metabolite, AR-C124910XX, which is at least as potent at the $P2Y_{12}$ receptor as ticagrelor; it is present in the circulation at approximately one-third of the concentration of the parent drug (Husted et al., 2006). In healthy human subjects and patients with stable atherosclerosis, the pharmacokinetics of ticagrelor are linear and predictable over a wide dose range (Husted et al., 2006; Teng and Butler 2008, 2010; Butler and Teng 2010). Data from preclinical studies (rat and marmoset) have shown that ticagrelor is predominantly excreted via feces with minor renal elimination (Astra Zeneca, data on file).

To elucidate the exact disposition and metabolism of ticagrelor in humans, the present study was undertaken in healthy volunteers, using a single oral dose of radiolabeled ticagrelor. Pharmacokinetic data are reported for ticagrelor and its active metabolite AR-C124910XX. In addition, the metabolic profile of ticagrelor and the main metabolites present in plasma and excreted in urine and feces are identified.

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ABBREVIATIONS: AZD6140, (1*S*,2*S*,3*R*,5*S*)-3-[7-[[(1*R*,2*S*)-2-(3,4-difluorophenyl)cyclopropyl]amino]-5-(propylthio)-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidin-3-yl]-5-(2-hydroxyethoxy)-1,2-cyclopentanediol); HPLC, high-performance liquid chromatography; LSC, liquid scintillation counting; LC, liquid chromatography; MS/MS, mass spectrometry; AUC, area under the concentration-time curve.

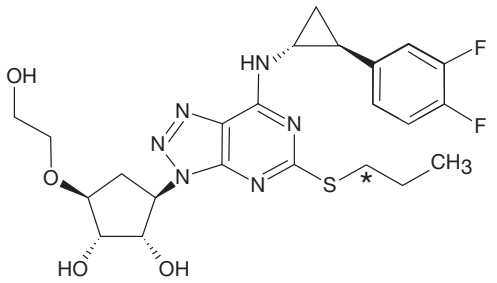

FIG. 1. Structure of ^{14}C-radiolabeled ticagrelor (the asterisk indicates the site of the radiolabel).

Materials and Methods

Radiolabeled Drugs and Chemicals. Ticagrelor, AR-C124910XX, and AR-C133913XX were supplied by AstraZeneca Pharmaceuticals (Wilmington, DE, or Loughborough, Leicestershire, UK). [^{14}C]Ticagrelor oral suspension (Fig. 1) (radiochemical purity 97%) was manufactured by GE Healthcare (Little Chalfont, Buckinghamshire, UK). All reagents were of analytical or high-performance liquid chromatography (HPLC) grade.

Study Design and Subjects. This was an open-label, single-dose, nonrandomized study carried out at a single center (study D5130C000130; Alderley Park Clinical Pharmacology Unit, AstraZeneca R&D Alderley Park, Macclesfield, Cheshire, UK). Written informed consent was obtained from all volunteers before initiation of the study. The study was performed in accordance with the ethical principles established by the Declaration of Helsinki and was consistent with ICH/Good Clinical Practice, applicable regulatory requirements (including local ethical review board approval), and the AstraZeneca policy on bioethics.

Six healthy male subjects (aged 40–55 years) were enrolled in the study. The health status of each volunteer was determined during a screening visit (visit 1) based on medical history, physical examination, electrocardiogram, and clinical laboratory test results. Subjects were excluded if they had participated in studies involving radiolabeled substances in the past 12 months or were monitored for radioactivity as part of their job; had symptoms of clinically relevant illness; had any disease or condition known to interfere with the absorption, distribution, metabolism, or excretion of drugs; had severe allergic disease; or had demonstrated hypersensitivity to any drugs related structurally or mechanistically to ticagrelor.

Within 21 days of the screening visit, fasted subjects (no food for 12 h overnight) received a single oral dose of 200 mg of [^{14}C]ticagrelor as a 10-g oral suspension (222.7 kBq/g). Subjects remained in an upright position (standing, sitting, or semirecumbent) without food for at least 4 h after administration of the dose. Subjects remained on site for the next 168 h (7 days). Subjects were monitored for the incidence of any causally related or serious adverse events and for clinically significant changes in electrocardiogram, blood pressure, heart rate, or laboratory safety variables in blood or urine throughout the treatment period and at follow-up (7–14 days postdose).

Collection and Storage of Blood and Plasma Samples. Blood samples (6 ml), for measurement of total radioactivity in whole blood and plasma and of ticagrelor and AR-C1249910XX in plasma, were collected predose and at various times up to 168 h postdose. For metabolite profiling, additional 20-ml plasma samples were collected in lithium heparin tubes at 1, 3, 12, and 24 h postdose. Pooled samples (all subjects) of plasma at 1, 1.5, 2, 3, 4, 6, 8, and 10 h (1–1.2 ml) postdose were also analyzed. Plasma samples were stored at −20°C or below and whole-blood samples at 4°C.

Collection and Storage of Urine and Fecal Samples. Urine samples were collected for determination of ticagrelor, AR-C124910XX, and total radioactivity. Urine collection intervals were at predose and 0 to 6, 6 to 12, and 12 to 24 h daily for 7 days postdose. Fecal samples were collected for determination of total radioactivity predose and then at 24-h intervals postdose. Samples were collected until two successive samples were shown to be <3 times background radiation or total recovery was ≥90%. Urine samples were stored at room temperature (15–25°C), and fecal samples were stored at −20°C.

Samples for metabolic profiling analysis were selected based on the level of radioactivity. The 6-h urine samples from each of the six volunteers were analyzed, and fecal subsamples (~5 g) were selected for volunteers 4 and 6 at 48 h, volunteers 3 and 5 at 72 h, and volunteers 1 and 2 at 96 h. Pooled samples (all subjects) of urine from 6 to 24 h (18.31 g), feces at various time points (time point selected if sample had >20,000 dpm) (15.70 g), and plasma at 1, 1.5, 2, 3, 4, 6, 8, and 10 h (1–1.2 ml) postdose were also analyzed.

Sample Preparation for LSC and HPLC Analysis. Urine samples were centrifuged at 3000 rpm for 10 min. Fecal samples were extracted 3 times with 3 ml/g acetonitrile-water (1:1, v/v), centrifuged (3000 rpm, 10 min), and then decanted. An aliquot of each extract (20 ml) was partitioned with hexane (3 × 20 ml) to remove fat. The hexane layers were removed and the extracts were concentrated under nitrogen and centrifuged (3000 rpm, 10 min), and duplicate aliquots were analyzed for liquid scintillation counting (LSC). Plasma samples were extracted with 3 ml/g acetonitrile-methanol (1:1, v/v), vortex-mixed, and stored at −20°C for 10 min to aid precipitation. Samples were centrifuged (3000 rpm, 10 min), and the supernatant was concentrated under nitrogen and decanted into Eppendorf tubes. Duplicate aliquots of all samples were taken for LSC before HPLC.

Bioanalytical Assay of Ticagrelor and AR-C124910XX. Ticagrelor and AR-C124910XX concentrations in urine and plasma were analyzed by York Bioanalytical Solutions (York, UK) using a separately validated liquid chromatography technique with tandem mass spectrometric detection (LC-MS/MS). For plasma analysis, mean intrabatch accuracy was 91.9 to 109.0 and 86.8 to 109.2%, for ticagrelor and AR-C124910XX, respectively; intrabatch precision was 4.0 to 8.4 and 5.2 to 16.9%, respectively. For urine analysis, mean intrabatch accuracy was 86.8 to 97.0 and 83.4 to 92.8% for ticagrelor and AR-C124910XX, respectively; intrabatch precision was 2.9 to 9.1 and 2.6 to 6.7%, respectively. Assay lower limits of quantification were 5.0 ng/ml for ticagrelor and 2.5 ng/ml for AR-C124910XX in plasma and 1.0 and 2.5 ng/ml, respectively, in urine.

Measurement of Total Radioactivity by Liquid Scintillation Counting. Total ^{14}C radioactivity in samples of blood and plasma (measured directly), feces (mechanically homogenized with water), and urine [diluted with acetonitrile (4:1 urine-acetonitrile, v/v), to ensure complete solubility of ticagrelor] was determined by LSC (Tri-Carb liquid scintillation analyzer; PerkinElmer Life and Analytical Sciences, Waltham, MA). Duplicate (or triplicate for feces) oxidized samples were analyzed for ^{14}C radioactivity and corrected for background activity using ^{133}Ba as external source, and disintegrations per minute values were calculated. A nominal 25 dpm above background was set as the limit of detection.

Pharmacokinetic Analysis. Pharmacokinetic analysis was done using WinNonlin (Pharsight, Mountain View, CA). Primary pharmacokinetic assessments for total radioactivity in plasma and blood included peak concentration (C_{max}), time to peak concentration (t_{max}), elimination half-life ($t_{1/2}$), area under the concentration-time curve from zero to the time of the last concentration above the limit of quantification (AUC_{0-t}), area under the concentration curve to infinity (AUC), and plasma/blood ratio, percent dose excreted in urine and feces, and total recovery (percent) of ^{14}C radioactivity. For ticagrelor and AR-C124910XX, pharmacokinetic measurements included C_{max}, t_{max}, $t_{1/2}$, AUC_{0-t}, AUC, total amount of drug/metabolite excreted in urine ($Ae_{(\infty)}$), and percent dose excreted in urine. In addition, renal clearance (CL_R) was calculated or estimated for ticagrelor. For AR-C124910XX, metabolite/parent C_{max} and AUC ratios were also calculated. The terminal elimination rate constant (λ_Z) was calculated by log-linear regression of the terminal portion of the plasma concentration-time profile using at least three time points, and $t_{1/2}$ was calculated as $0.693/\lambda_Z$. AUC_{0-t} was calculated using the linear trapezoidal method, and AUC was derived by extrapolation of the terminal elimination phase to infinity. CL_R was estimated as the ratio of total amount of ticagrelor or AR-C124910XX excreted unchanged in urine to ticagrelor or AR-C124910XX AUC.

Determination of Ticagrelor and Its Metabolites: HPLC Chromatographic Conditions for Radioactivity Profiling. Metabolic profiling and metabolite identification were performed by Charles River Laboratories (Tranent, Scotland). The plasma, urine, and fecal samples were analyzed for ticagrelor and its metabolites by HPLC (1100 series liquid chromatograph; Agilent Technologies, Santa Clara, CA) using on-line radiodetection (Radiomatic Flo-One 505TR flow scintillation analyzer; PerkinElmer Life and Analytical Sciences) for urine or feces or by fraction collection every 60 s (model 202 fraction collector; Gilson, Inc., Middleton, WI) and analysis by LSC (1600-TR; PerkinElmer Life and Analytical Sciences) for plasma. Ultra-

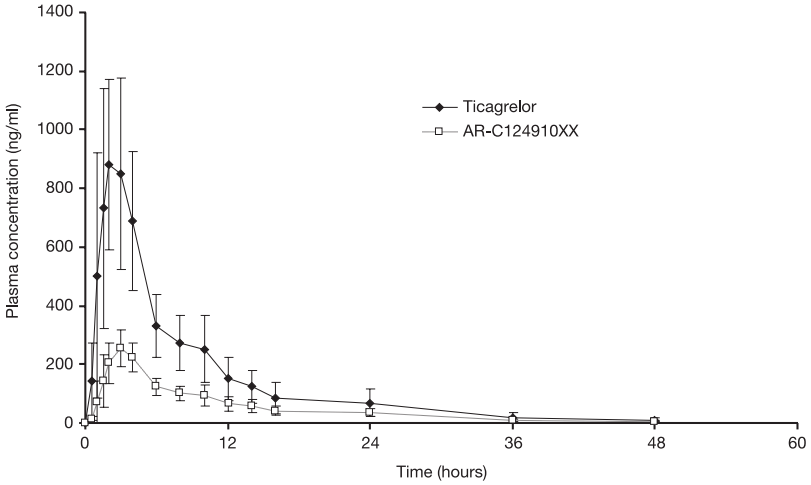

FIG. 2. Mean (±S.D.) plasma concentrations of ticagrelor and AR-C124910XX in healthy subjects ($n = 6$) after a single 200-mg oral dose of [^{14}C]ticagrelor.

violet detection was set at 254 nm. The HPLC column was an Ace 3 C18 (250 × 4.6 mm, 3 μm particle size), with a variable mobile phase consisting of 0.1% formic acid in Milli-Q water and acetonitrile; the percentage of acetonitrile was increased from 5 to 50% over 40 min and then to 95% at 45 min, where it was held for 3 min. The flow rate was 1.0 ml/min.

The retention time of ticagrelor (~42.5 min) was determined by running an aliquot of unlabeled ticagrelor [~1 mg/ml in 1:3 (v/v) acetonitrile-water] immediately before each batch of samples. The limit of quantification was defined as background level (mean of the first or last two fractions in each analytical run) plus 30 dpm of radioactivity, and plasma sample fractions containing less than this were not included in further calculations.

Validation of the HPLC System. The linearity of response of the radiodetector was considered acceptable (correlation coefficient 0.9991), as established by conducting a series of dilutions of [^{14}C]ticagrelor in mobile phase over the range 9000 to 135,000 dpm. The coefficient of variation (3.3%; acceptance criteria of <15%) for the reproducibility of the HPLC method was established by performing nine consecutive injections of [^{14}C]ticagrelor at approximately 50% of the linear range. An injection of mobile phase immediately after these injections demonstrated that there was no carryover of radioactivity. The recovery of radioactivity was 94.3% in urine, 95.7% in plasma, and 96.9% in feces. No significant degradation of [^{14}C]ticagrelor was observed during these analyses.

LC-MS/MS Analysis of Ticagrelor and Its Metabolites. The 6- to 24-h pooled urine samples and pooled fecal extract samples and the 3-h pooled plasma samples were analyzed for ticagrelor and its metabolites by LC-MS/MS [1100 series liquid chromatograph and Micromass Q-TOF micro Mass Spectrometer operating MassLynx software (version 4.0, SP 2; Waters, Milford, MA]. Radiochemical detection was performed with the Radiomatic 500TR series flow scintillation analyzer using Flo-One software (version 3.65). For LC, an injection volume of 10 to 250 μl was used with a split to the mass spectrometer of ~200 μl. MS was performed in positive ion electrospray ionization mode. Ticagrelor, AR-C124910XX, and AR-C133913XX were used as reference compounds.

For determination of sample radioactivity, duplicate aliquots of liquid samples were transferred to separate scintillation vials, diluted with water if necessary, and analyzed by LSC. Solid samples of fecal postextracted solids were weighed in duplicate into Combusticones (PerkinElmer Life and Analytical Sciences) with pads for combustion analysis (model 307 Tri-Carb Automatic Sample Oxidizer; PerkinElmer Life and Analytical Sciences). Combustion efficiency and carryover were assessed at the start of each run of 30 samples by combusting blanks and quality control standards containing Spec-Check ^{14}C. Throughout the analysis, combustion efficiency was >97%. All samples were counted for 5 min with representative blanks using a 1600-TR liquid scintillation analyzer with automatic quench correction by external channel ratio. The representative blank sample values were subtracted from sample disintegrations per minute to give net disintegrations per minute per sample.

Results

Six healthy male subjects with mean age of 45.7 years (range 41–54 years), mean body weight of 78.9 kg (63.3–91.0 kg), and mean body mass index of 25.8 kg/m^2 (23.7–29.4 kg/m^2) enrolled and completed the study. The 200-mg oral dose of [^{14}C]ticagrelor was well tolerated, with no serious adverse events reported. There were no clinically important changes in laboratory parameters, vital signs, electrocardiograms, or physical findings.

Pharmacokinetics. Ticagrelor was rapidly absorbed, with median t_{max} observed at 1.5 h. The active metabolite AR-C124910XX appeared rapidly in the plasma, with median t_{max} observed at 3.0 h (Fig. 2; Table 1). Plasma half-life was approximately 8 and 12 h for ticagrelor and

TABLE 1

Pharmacokinetic parameters for ticagrelor, AR-C124910XX, and total radioactivity in plasma and whole blood in healthy male subjects (n = 6) after a single oral dose of 200 mg of [^{14}C]ticagrelor

Data for t_{max} are median (range), data for C_{max}, AUC_{0-t}, and AUC are geometric mean (coefficient of variation percent), and all other data are mean (SD). Units for radioactivity are nanogram equivalents per milliliter for C_{max} and nanogram equivalents per hour per milliliter for AUC_{0-t} and AUC.

Parameter	Ticagrelor	AR-C124910XX	Plasma ^{14}C	Blood ^{14}C
t_{max} (h)	1.5 (1.0–3.0)	3.0 (2.0–3.0)	2.5 (2.0–3.0)	3.0 (2.0–4.0)
C_{max} (ng/ml)	923 (35.6)	264 (22.0)	1534 (21.0)	1129 (17.0)
AUC_{0-t} (ng · h/ml)	6591 (44.8)	2477 (28.4)	9007 (34.1)	5331 (15.2)
AUC (ng · h/ml)	6675 (44.7)	2538 (28.4)	11,042 (35.4)	7132 (18.1)
$t_{1/2}$ (h)	8.4 (2.3)	11.5 (4.5)	6.3 (4.1)	4.6 (2.2)
$Ae_{(\infty)}$ (μg)	41.5 (22.9)	81.3 (21.4)		
CL_R (l/h)	0.00584 (0.00252)	NQ		
Metabolite/parent C_{max} ratio		0.29 (0.064)		
Metabolite/parent AUC ratio		0.40 (0.124)		

NQ, nonquantifiable (below limit of quantification).

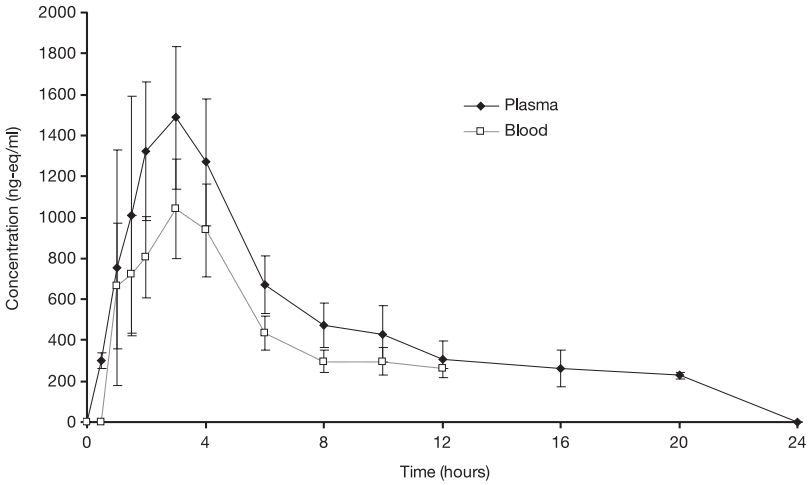

FIG. 3. Mean (±S.D.) concentrations of total ^{14}C radioactivity in plasma and whole blood in healthy subjects ($n = 6$) after a single 200-mg oral dose of [^{14}C]ticagrelor.

AR-C124910XX, respectively. Exposure to AR-C124910XX was 29% that of the parent compound at peak levels and 40% overall. Amounts of unchanged ticagrelor and AR-C124910XX excreted in the urine accounted for 0.02 and 0.04% of the total dose, respectively. Median t_{max} for total radioactivity was 2.5 h in plasma and 3.0 h in whole blood (Fig. 3). Radioactivity concentrations declined steadily thereafter, and in most subjects were not quantifiable in plasma after 20 h and in whole blood after 12 h. The geometric mean AUC_{0-t} ratio of total radioactivity in plasma/whole blood was 1.69, indicating that ticagrelor and its metabolites are largely restricted to the plasma space. The mean recovery of total radioactivity from both urine and feces was 84.3 ± 5.5% (±S.D.) of the dose, consisting of 57.8 ± 4.4% in the feces and 26.5 ± 4.1% in the urine. The majority of radioactivity was recovered in urine by 12 h and in feces by 96 h (Fig. 4).

Radioprofiling of Individual and Pooled Samples. HPLC chromatograms of the pooled plasma samples from all six subjects showed that the major peak at all time points up to 6 h (1, 1.5, 2, 3, 4, and 6 h) was the parent compound ticagrelor (retention time 43 min) (Fig. 5A). However, LC-MS/MS analysis confirmed that the peak comprised both ticagrelor and the major metabolite AR-C124910XX (M8) (Table 2). This same peak was also present in the 10-h pooled plasma sample (0.132 μg Eq/g), although an additional peak (M2; retention time 18 min) was larger (0.168 μg Eq/g) (Fig. 5B). Minor peaks of radioactivity (≤0.354 μg Eq/g) were also identified at 1.5, 2, and 3 h, which LC-MS/MS analysis confirmed as being metabolites M1, M2, M5 (AR-C133913XX), and M7 (Table 2). Individual radiochromatograms from individual subjects were qualitatively and quantitatively consistent for all subjects and time points.

Radiochromatograms obtained from the 6- to 24-h pooled urine sample are shown in Fig. 6, and quantitative distributions of the metabolites in the samples are shown in Table 3. Radioactivity excreted in urine accounted for 22.7% of the dose. Chromatograms for 6-h urine samples from each subject and the pooled urine sample were qualitatively consistent, with minor quantitative differences. In urine, the major peak was identified as M5 (AR-C133913XX; retention time 24.3 min), which accounted for 9.21% of the total dose, and a second major peak was identified as M4 (retention time 22.4 min), accounting for 6.64% of the dose. Additional peaks between 14 and 21 min were identified as M1, M2, and M3 (each <2% of the dose), and a small peak at 37.7 min represented M6, M9, and M10 combined (<6.64% of dose).

Radiochromatograms obtained from the pooled fecal sample are shown (Fig. 6), with quantitative distributions of the metabolites in Table 3. Radioactivity excretion in feces accounted for 54.8% of the dose. Chromatograms for fecal samples were qualitatively and quantitatively consistent for all subjects and time points. The major peaks in feces had retention times of 42.7 and 42.0 min, representing ticagrelor (27.09% of dose), and AR-C124910XX (M8; 21.73% of dose), respectively. Additional minor peaks were present at 24.4 min (M5) and 33.4 min (M7).

Identification of Metabolites in Urine, Feces, and Plasma. LC-MS/MS analysis identified 10 discrete metabolites from pooled urine (6–24 h), pooled feces, and pooled plasma (3 h) matrices samples

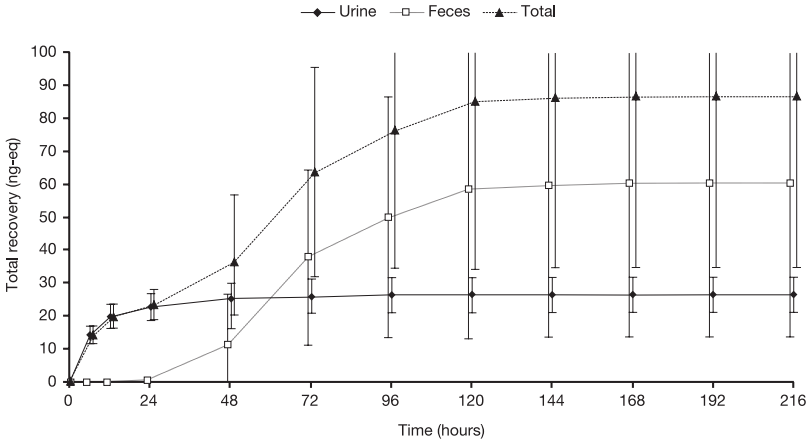

FIG. 4. Mean recovery (±S.D.) of total radioactivity in urine (◆) and feces (□) (0–168 h) and total recovery (▲) from healthy subjects ($n = 6$) after a single 200-mg oral dose of [^{14}C]ticagrelor. ◆, urine; □, feces; ▲, total.

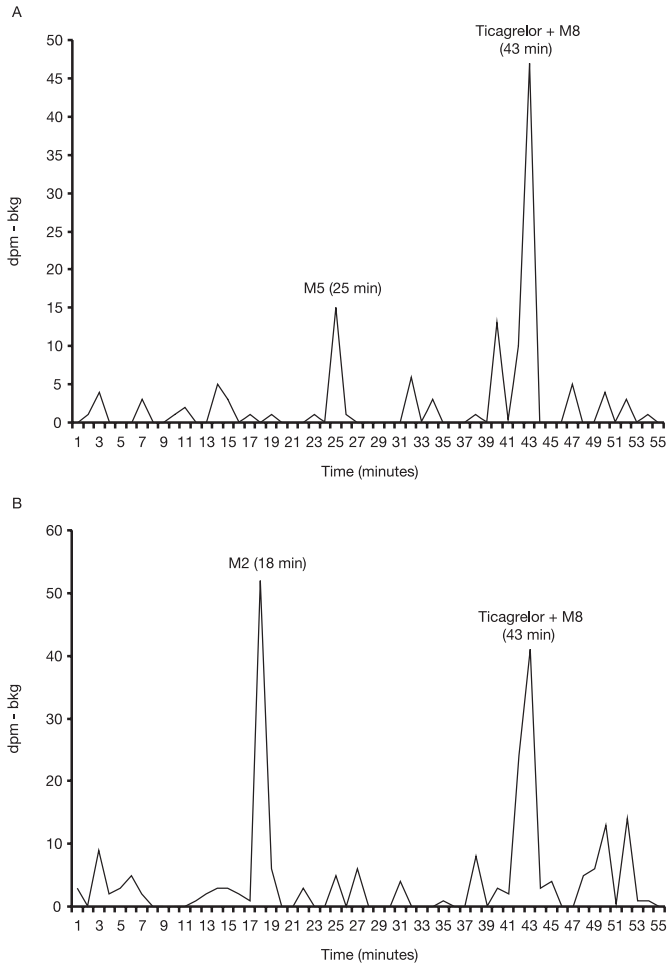

FIG. 5. HPLC radiochromatograms of pooled plasma at 3 h (A), and 10 h (B) in healthy subjects ($n = 6$) after a single 200-mg oral dose of [^{14}C]ticagrelor. bkg, background.

(Table 4). Analysis of ticagrelor (*m*/*z* 523), AR-C124910XX (M8, *m*/*z* 479), and AR-C133913XX (M5, *m*/*z* 371) reference standards demonstrated that the structures were consistent with those previously elucidated. Product ion spectra of each radiolabeled peak were used to characterize the probable structure of each metabolite.

In urine there were two major radiolabeled peaks designated M4 (22.3 min, *m*/*z* 547) and M5 (24.3 min, *m*/*z* 371) (Fig. 7). The product ion spectrum of the ion *m*/*z* 547 showed major ions at 371, 343, 183, and 141 (Fig. 7A). An intense ion at *m*/*z* 371 indicated the loss of glucuronide (−176 Da), suggesting that the metabolite M4 is a glucuronide in which the difluorophenylcyclopropyl moiety has been lost. The exact position of glucuronidation is unknown, but the proposed structure is illustrated in Fig. 7A. The metabolite M5 had the same retention time (24.3 min) and full scan and product ion mass spectra properties ($[M + H]^+$ at *m*/*z* 371) as reference standard AR-C133913XX (Fig. 7B).

Several minor urinary metabolites were also identified [M1 (13.9 min, *m*/*z* 387), M2 (14.3 min, *m*/*z* 387), and M3 (20.2 min, *m*/*z* 503)], and their tentative structures are identified in the proposed metabolic profile for ticagrelor (Fig. 8). These data suggest that M2 is formed by the loss of the difluorophenylcyclopropyl side chain from ticagrelor followed by oxidation and that M1 may be an isomer of M2. M3 is proposed as a glucuronide of ticagrelor in which both the difluorophenylcyclopropyl side chain and the hydroxyethyl side chain have been cleaved, although the exact site of glucuronidation remains unknown. MS analysis of the radiopeak at ~36.7 min showed multiple related urinary metabolites (designated M6, M9, and M10). The full spectra for metabolites M6 (36.8 min, *m*/*z* 655) and M9 (37.1 min, *m*/*z* 699) showed other intense ions at *m*/*z* 479, and *m*/*z* 523, respectively, indicating loss of glucuronide, which suggested that M6 and M9 were the glucuronidated parent compound after cleavage of the hydroxyethyl side chain. M10 (37.3 min, *m*/*z* 539) was considered to be the parent molecule that has undergone monohydroxylation in the cyclopentoxy ethanol moiety. This characterization is supported by the presence of an ion at *m*/*z* 363, indicating an intact triazolopyrimidine core, propyl side chain, and difluorophenylcyclopropyl group and an ion at *m*/*z* 153, also indicating an intact difluorophenylcyclopropyl moiety. The proposed structures of metabolites M6, M9, and M10 are identified in the proposed metabolic profile for ticagrelor (Fig. 8).

Spectral analysis of the pooled fecal sample showed two major radiolabeled components at retention times 41.5 min (*m*/*z* 523) and 40.9 min (*m*/*z* 479), corresponding to the reference standards ticagrelor and AR-C124910XX (M8), respectively (Table 4). One minor peak at 24.3 min (*m*/*z* 371) was identified as corresponding to the reference standard AR-C133913XX (M5). Another minor peak was designated M7 (32.7 min, *m*/*z* 495). On the basis of other ions identified in the spectrum (*m*/*z* 477, indicating a facile loss of H_2O; *m*/*z* 449, indicating loss of N_2 from the triazolopyrimidine core; and *m*/*z* 153, indicating an intact difluorophenylcyclopropyl moiety), this metabolite was assigned as the parent molecule that had lost the hydroxyethyl side chain and undergone further oxidation. Oxidation may occur in the propyl side chain, possibly β to the sulfur, as suggested by the facile loss of H_2O.

Radioactivity levels in the 3-h plasma samples were not high enough to permit a concurrent radiochromatogram. Reconstructed chromatograms based on HPLC fraction collection/LSC data from the radioprofiling phase showed two peaks at ~43 and ~25 min that had similar retention times and full scan and ion spectra properties to be ticagrelor/AR-C124910XX (M8) and AR-C133913XX (M5) peaks,

TABLE 2

Concentration of ticagrelor and metabolites over time in pooled plasma samples from healthy male subjects (n = 6) after a single oral dose of 200 mg of [^{14}C]ticagrelor

	Metabolite at Time Postdose							
	1 h	1.5 h	2 h	3 h	4 h	6 h	8 h[a]	10 h
				μg Eq/g				
M1		0.185						
M2			0.146					0.168
M5 (AR-C133913XX)				0.354				
M7		0.101						
Ticagrelor + M8 (AR-C124910XX)	0.754	0.319	0.710	0.546	0.715	0.433		0.132

[a] Below the limit of quantification for the 8-h sample.

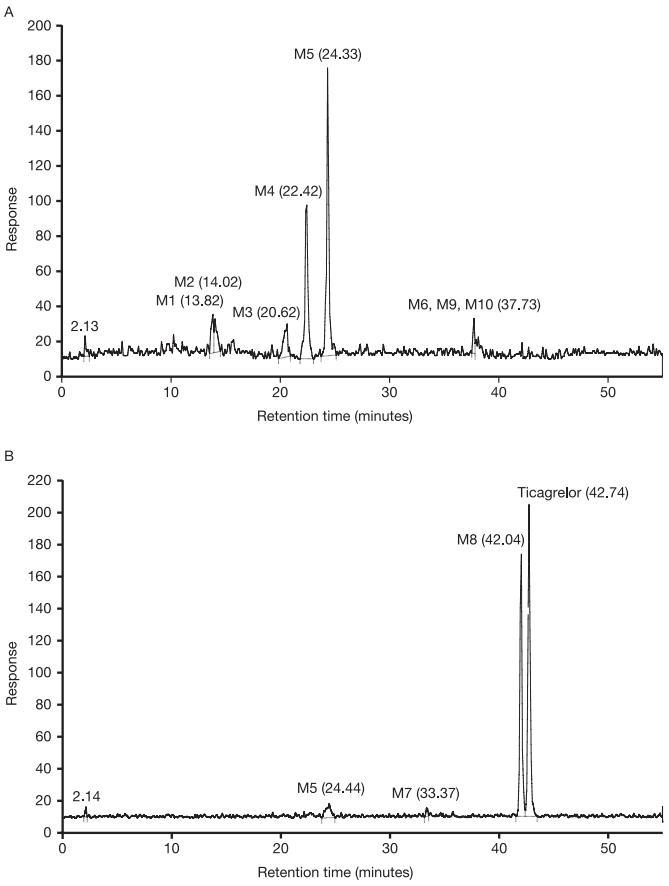

FIG. 6. On-line radiochromatograms of a pooled 6- to 24-h urine sample (A) and pooled fecal extract sample (B) from healthy subjects ($n = 6$) after a single 200-mg oral dose of [^{14}C]ticagrelor.

respectively, identified in other sample matrices and in the reference standards.

Discussion

The present study characterizes the pharmacokinetics and proposed metabolic pathways involved in the excretion of a single oral dose of 200 mg of [^{14}C]ticagrelor in healthy male subjects. Our findings showed that ticagrelor is rapidly absorbed and extensively metabolized in humans, with a total of 10 metabolites characterized by LC-MS from plasma, urine, and feces.

Absorption of ticagrelor was rapid, concordant with previous data showing that the onset of the antiplatelet effect of ticagrelor is approximately 30 min after oral administration (Gurbel et al., 2009; Tapp et al., 2010). The major circulating components in plasma were ticagrelor and its active metabolite AR-C124910XX (M8), consistent with previous plasma concentration data and pharmacokinetic parameters of ticagrelor and AR-C124910XX (Husted et al., 2006; Teng and Butler 2008, 2010; Butler and Teng 2010). Ticagrelor reached a maximal mean concentration at 1.5 h and then was rapidly metabolized, with a terminal elimination half-life of approximately 8 h. AR-C124910XX reached a maximal mean concentration at 3 h, with

TABLE 3

Retention times of ticagrelor and its metabolites and percentage of radioactive dose in pooled urine and feces samples from healthy subjects ($n = 6$) after a single oral dose of 200 mg of [^{14}C]ticagrelor

	Urine (22.7% of Dose)		Feces (54.8% of Dose)	
Metabolite	Retention Time, min	%Dose	Retention Time	%Dose
	min		*min*	
M1	13.8	1.32		
M2	14.0	1.32		
M3	20.6	1.91		
M4	22.4	6.64		
M5 (AR-C133913XX)	24.3	9.21	24.4	2.77
M7			33.4	0.61
M8 (AR-C124910XX)			42.0	21.73
Ticagrelor			42.7	27.09

TABLE 4

Metabolites of ticagrelor identified by LC-MS analysis of reference standards and metabolites in pooled urine (6–24 h), pooled feces, and pooled plasma (3 h) from healthy subjects ($n = 6$) after a single oral dose of 200 mg of [^{14}C]ticagrelor

Metabolite	$[M + H]^+$	Product Ions m/z[a]
Reference standards		
Ticagrelor[b,c]	523	**495, 453,** 363, 321, 335, 293, 153, 127
M5 (AR-C133913XX)[b,c,d]	371	301, 263, 221, 183, 169, 141
M8 (AR-C124910XX)[b,c]	479	363, 335, 321, 293, 153, 127
Other metabolites		
M1[d]	387	N.D.
M2[d]	387	N.D.
M3[d]	503	327, 211, 141
M4[d]	547	371, 343, 183, 141
M6[d]	655	479
M9[d]	699	523, 495
M10[d]	539	363, 153
M7[b]	495	477, 449, 361, 153

N.D., no data.
[a] Ions in boldface represent those only identified with ticagrelor as reference standard.
[b] Present in feces.
[c] Present in plasma.
[d] Present in urine.

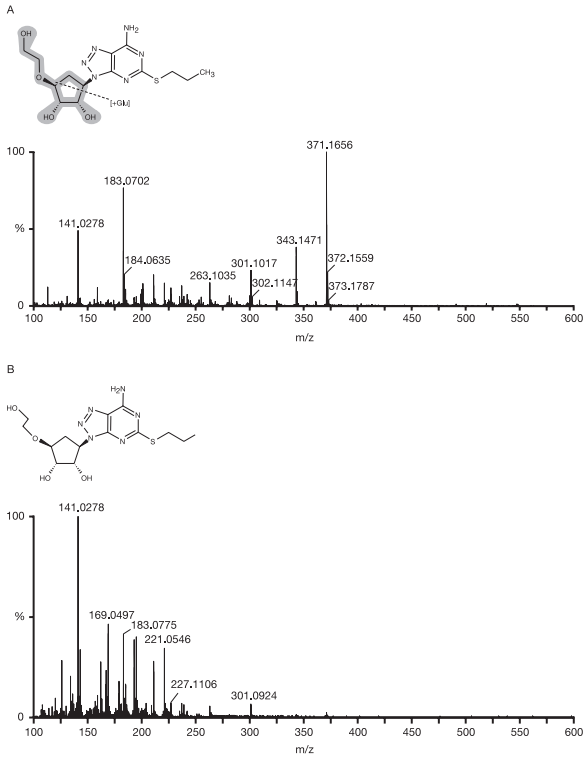

FIG. 7. Mass spectrum of the two major metabolites M4 (A) and M5 (B) from a pooled 6- to 24-h urine sample from healthy subjects ($n = 6$) after a single 200-mg oral dose of [^{14}C]ticagrelor. A, metabolite M4. Fragment ions derived from M4 (m/z 547): 371, 343, 183, and 141. B, metabolite M5 (AR-C133913XX). Fragment ions derived from M5 (m/z 371):301, 221, 183, 169, and 141.

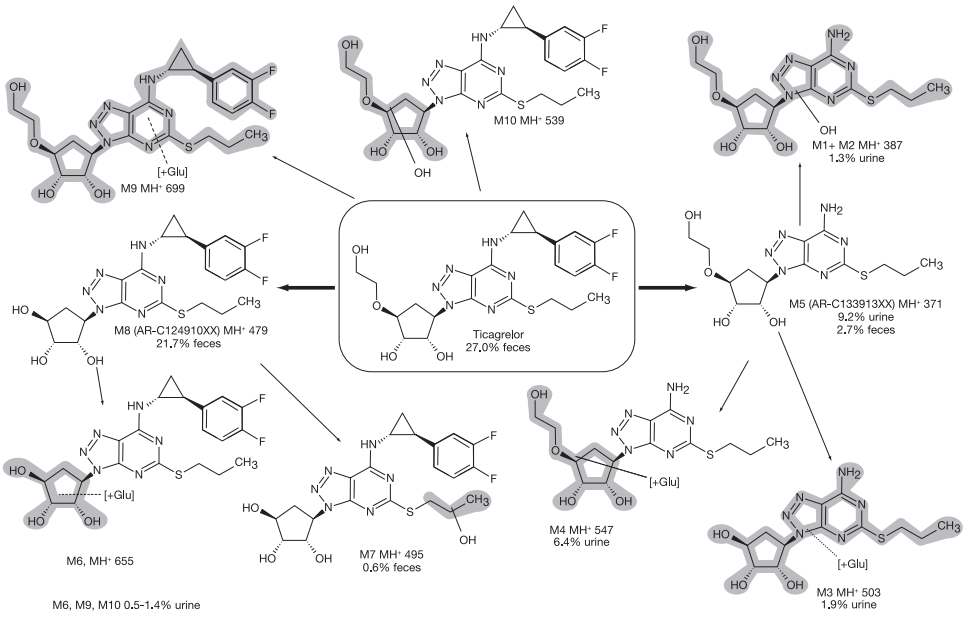

FIG. 8. Proposed metabolic pathway for the formation and elimination of ticagrelor metabolites (shadowed areas indicate possible sites of biotransformation). The proportion of the dose of [^{14}C]ticagrelor identified as these metabolites in urine or feces is indicated.

a mean plasma half-life of 12 h. Both ticagrelor and its active metabolite, AR-C124910XX, had undetectable concentrations by 48 h postdose.

Previous studies have shown that the extent of platelet inhibition is dependent on the concentration of drug/metabolite available to bind to platelets, closely reflecting plasma concentrations of ticagrelor + AR-C124910XX (Peters and Robbie, 2004; Husted et al., 2006; Peters et al., 2006). Thus, changes in the plasma concentrations of ticagrelor and AR-C124910XX would be expected to affect antiplatelet activity. However, the drug and the metabolite are equipotent (AstraZeneca, data on file); thus, it is considered that the majority of the antiplatelet effect of ticagrelor is due to the parent compound because AR-C124910XX is present at a concentration approximately 40% (29% at peak concentration) of that of the parent drug.

In contrast with the thienopyridines, which require metabolic activation to exert their antiplatelet effect, the parent compound having most of the activity of ticagrelor will have different implications for drug interactions. It is proposed that AR-C124910XX, the major and active metabolite, is formed from ticagrelor via probable oxidative loss of the parent hydroxyethyl side chain. In vitro experiments with human liver microsomes have shown that ticagrelor is metabolized by CYP3A4/5 isoforms (AstraZeneca, data on file). Thus, there is a potential for drug-drug interactions with ticagrelor. However, although ticagrelor and ARC124910XX plasma levels are likely to change during concomitant administration of CYP3A inhibitors, it is anticipated that the overall antiplatelet activity would not be decreased (but may be increased) because ticagrelor acts directly. In contrast, the antiplatelet activity of the prodrug clopidogrel is diminished in the presence of CYP3A inhibitors, because conversion to its active metabolite occurs via a series of cytochrome P450 enzymes, including CYP2C19 and CYP3A (Farid et al., 2007).

Radiochromatograms of both urine and fecal samples showed low intersubject variability with only small quantitative differences in the metabolic profiles across each of the six volunteers. Although this small study did not examine whether any genetic polymorphisms exist in the metabolic biotransformation of ticagrelor, our findings combined with those from earlier studies (Husted et al., 2006; Peters et al., 2006) suggest there is likely to be low variability in antiplatelet response with ticagrelor. In contrast, variability in the response to clopidogrel (Mega et al., 2009), partially due to the genetic variation of cytochrome P450 2C19 (Varenhorst et al., 2009), has led to an US Food and Drug Administration boxed warning for poor metabolizers (FDA announces new boxed warning on Plavix: alerts patients, health care professionals to potential for reduced effectiveness, http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm204253.htm). Because ticagrelor and ARC124910XX are equipotent (AstraZeneca, data on file) and ticagrelor does not require metabolism for activity, genetic polymorphisms in cytochrome P450s are unlikely to have an impact on its activity.

Overall recovery of total radioactivity from a single 200-mg oral dose was 84.3%. Most of this radioactivity was recovered [as ticagrelor and AR-C124910XX (M8)] in the feces, suggesting that the parent ticagrelor has low absorption or that these components have undergone either biliary or intestinal excretion. Ticagrelor and AR-C124910XX may have passed directly into the bile from the liver or may have been transported by intestinal P-glycoprotein and thereby were secreted from the systemic circulation into the intestine. In this study we were unable to differentiate between these two proposed mechanisms. Measurement of the AUC_{0-t} ratio of total radioactivity in plasma relative to that in whole blood was 1.69, indicating that ticagrelor and its metabolites are largely restricted to the plasma space and unlikely to extensively penetrate or bind to erythrocytes.

Metabolism was extensive as indicated by the minor amounts of unchanged ticagrelor and AR-C124910XX excreted in urine compared with total radioactivity recovered in urine (less than 0.05% of the dose compared with total radioactivity recovery of 26.5% in the urine). Although AR-C133913XX (M5) was only present at lower levels and was undetectable in plasma after 8 h, this metabolite was the major component in the pooled urine sample. Our findings suggest that an oxidative pathway leads to *N*-dealkylation of ticagrelor, resulting in the major urinary metabolite AR-C133913XX (M5) by loss of a difluorophenylcyclopropyl group; the enzyme involved in this pathway has not been identified.

Glucuronidation of ticagrelor, AR-C124910XX, and AR-C133913XX by UDP-glucuronosyltransferase formed the more polar M9, M6, and M4 metabolites, respectively. An additional glucuronidated metabolite was formed from AR-C133913XX by initial loss of the hydroxyethyl side chain followed by conjugation with glucuronic acid to form metabolite M3. In line with these metabolites being highly polar, they are expected

to be rapidly excreted in urine and are, therefore, unlikely to have any significant pharmacological activity.

The minor metabolites M1 and M2 (found in urine) were formed via hydroxylation of AR-C133913XX, and metabolite M10 (a minor metabolite in urine) was formed via hydroxylation of ticagrelor. In addition, a minor metabolite in feces (M7) was formed by hydroxylation of AR-C124910XX. The isozymes responsible for these oxidative reactions have not been characterized. However, given that these metabolites are minor, the pharmacological relevance of these biotransformations is likely to be minimal. Furthermore, because there were minimal amounts of the active ticagrelor and AR-C124910XX in urine, our data therefore suggest that renal impairment may have minimal effects on systemic exposure to ticagrelor and its active metabolite, and, thus, on the antiplatelet effect of ticagrelor.

Total radioactivity recovery was 84.3%, with recovery from two subjects falling below 80%. The reason for the lower recovery of the radiolabeled drug is unknown. Previous absorption, distribution, metabolism, and excretion studies with a low recovery have been explained by the long half-life of the drug. However, given that ticagrelor and AR-C124910XX have a half-life of no more than 12 h, it may be that lower recovery is the result of limitations of the procedure rather than the pharmacology of the drug.

The metabolite profile of ticagrelor in humans is similar to that in rats and marmosets with comparable levels of circulating metabolites and the two major metabolites being AR-C124910XX and AR-C133913XX (AstraZeneca, data on file). Preclinical studies evaluating the toxicology of ticagrelor in mice, rats, and marmosets also showed that AR-C124910XX was observed as a major metabolite in these models. Exposures to ticagrelor and AR-C124910XX in these models exceeded those observed in humans and provided adequate safety margins for the toxicities seen.

In the pooled plasma samples, five metabolites were identified: AR-C124910XX (M8), AR-C133913XX (M5), and metabolites M1, M2, and M7 (metabolites M3, M4, M6, and M9 were only identified in urine and M10 was only identified in feces). However, previous data have shown that AR-C133913XX plasma concentrations were only quantifiable at the maximum tolerated dose or higher (900 and 1200 mg of ticagrelor) (AstraZeneca, data on file). Furthermore, in this study concentrations of M1, M2, and M7 were much lower than that of AR-C133913XX. Consequently, because plasma concentrations of M1, M2, and M7 are not expected to be quantifiable at the proposed therapeutic dose (90 mg of ticagrelor b.i.d.), pharmacological activity has only been evaluated for metabolites AR-C124910XX and AR-C133913XX (showing that AR-C124910XX but not AR-C133913XX has activity) (AstraZeneca, data on file). In addition, to aid further characterization of ticagrelor and its metabolites, AR-C124910XX and AR-C133913XX, a rapid and sensitive analytical method using liquid chromatography with tandem mass spectrometry has been developed (Sillén et al., 2010).

In conclusion, in humans ticagrelor is rapidly absorbed and extensively metabolized. The majority of the drug was detected in feces as ticagrelor and AR-C124910XX, whereas in urine, these were very minor components with the major metabolite being AR-C133913XX. Interindividual variability was small in both urine and fecal extracts with only small quantitative differences. All 10 of the detected metabolites were fully or partially characterized, and a full biotransformation pathway was proposed.

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References

Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Aviles F, Fox KA, Hasdai D, Ohman EM, Wallentin L, et al. (2007) Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* **28:**1598–1660.

Butler K and Teng R (2010) Pharmacokinetics, pharmacodynamics and safety and tolerability of multiple ascending doses of ticagrelor in healthy volunteers. *Br J Clin Pharmacol*, **70:**65–77.

Cannon CP, Husted S, Harrington RA, Scirica BM, Emanuelsson H, Peters G, Storey RF, and DISPERSE-2 Investigators (2007) Safety, tolerability, and initial efficacy of AZD6140, the first reversible oral adenosine diphosphate receptor antagonist, compared with clopidogrel, in patients with non-ST-segment elevation acute coronary syndrome: primary results of the DISPERSE-2 trial. *J Am Coll Cardiol* **50:**1844–1851.

Farid NA, Payne CD, Small DS, Winters KJ, Ernest CS 2nd, Brandt JT, Darstein C, Jakubowski JA, and Salazar DE (2007) Cytochrome P450 3A inhibition by ketoconazole affects prasugrel and clopidogrel pharmacokinetics and pharmacodynamics differently. *Clin Pharmacol Ther* **81:**735–741.

Gurbel PA, Bliden KP, Butler K, Tantry US, Gesheff T, Wei C, Teng R, Antonino MJ, Patil SB, Karunakaran A, et al. (2009) Randomized double-blind assessment of the ONSET and OFFSET of the antiplatelet effects of ticagrelor versus clopidogrel in patients with stable coronary artery disease: the ONSET/OFFSET study. *Circulation* **120:**2577–2585.

Husted S, Emanuelsson H, Heptinstall S, Sandset PM, Wickens M, and Peters G (2006) Pharmacodynamics, pharmacokinetics, and safety of the oral reversible $P2Y_{12}$ antagonist AZD6140 with aspirin in patients with atherosclerosis: a double-blind comparison to clopidogrel with aspirin. *Eur Heart J* **27:**1038–1047.

James S, Akerblom A, Cannon CP, Emanuelsson H, Husted S, Katus H, Skene A, Steg PG, Storey RF, Harrington R, et al. (2009) Comparison of ticagrelor, the first reversible oral $P2Y_{12}$ receptor antagonist, with clopidogrel in patients with acute coronary syndromes: rationale, design, and baseline characteristics of the PLATelet inhibition and patient Outcomes (PLATO) trial. *Am Heart J* **157:**599–605.

Mega JL, Close SL, Wiviott SD, Shen L, Hockett RD, Brandt JT, Walker JR, Antman EM, Macias W, Braunwald E, et al. (2009) Cytochrome p-450 polymorphisms and response to clopidogrel. *N Engl J Med* **360:**354–362.

Peters G, Butler K, Winter HR, and Mitchell PD (2006) Multiple-dose pharmacokinetics (PK) and pharmacodynamics (PD) of the reversible, orally active ADP receptor antagonist AZD6140. *Eur Heart J* **27 (Suppl 1):**758.

Peters G and Robbie G (2004) Single dose pharmacokinetics and pharmacodynamics of AZD6140. *Haematologica* **89 (Suppl 7):**14–15.

Sillén H, Cook M, and Davis P. Determination of ticagrelor and two metabolites in plasma samples by liquid chromatography and mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* doi: 10.1016/j.jchromb.2010.06.018.

Springthorpe B, Barton P, Birkinshaw TN, Bonnert RV, Brown RC, Chapman D, Dixon J, Guile SD, Humphries RG, et al. (2007) From ATP to AZD6140: the discovery of an orally active reversible $P2Y_{12}$ receptor antagonist for the prevention of thrombosis. *Bioorg Med Chem Lett* **17:**6013–6018.

Storey RF, Husted S, Harrington RA, Heptinstall S, Wilcox RG, Peters G, Wickens M, Emanuelsson H, Gurbel P, Grande P, et al. (2007) Inhibition of platelet aggregation by AZD6140, a reversible oral $P2Y_{12}$ receptor antagonist, compared with clopidogrel in patients with acute coronary syndromes. *J Am Coll Cardiol* **50:**1852–1856.

Tapp L, Shantsila E, and Lip GY (2010) Role of ticagrelor in clopidogrel nonresponders: resistance is futile? *Circulation* **121:**1169–1171.

Task Force for Diagnosis and Treatment of Non-ST-Segment Elevation Acute Coronary Syndromes of European Society of Cardiology, Bassand JP, Hamm CW, Ardissino D, Boersma E, Budaj A, Fernández-Avilés F, Fox KA, Hasdai D, Ohman EM, et al. (2007) Guidelines for the diagnosis and treatment of non-ST-segment elevation acute coronary syndromes. *Eur Heart J* **28:**1598–1660.

Teng R and Butler K (2008) AZD6140, the first reversible oral platelet $P2Y_{12}$ receptor antagonist, has linear pharmacokinetics and provides near complete inhibition of platelet aggregation, with reversibility of effect, in healthy subjects. *Can J Clin Pharmacol* **15:**e426.

Teng R and Butler K (2010) Pharmacokinetics, pharmacodynamics, tolerability and safety of single ascending doses of ticagrelor, a reversibly binding oral $P2Y_{12}$ receptor antagonist, in healthy subjects. *Eur J Clin Pharmacol* **66:**487–496.

van Giezen JJ and Humphries RG (2005) Preclinical and clinical studies with selective reversible direct $P2Y_{12}$ antagonists. *Semin Thromb Hemost* **31:**195–204.

Varenhorst C, James S, Erlinge D, Brandt JT, Braun OO, Man M, Siegbahn A, Walker J, Wallentin L, Winters KJ, et al. (2009) Genetic variation of CYP2C19 affects both pharmacokinetic and pharmacodynamic responses to clopidogrel but not prasugrel in aspirin-treated patients with coronary artery disease. *Eur Heart J* **30:**1744–1752.

Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, et al. (2009) Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* **361:**1045–1057.

Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK; Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators (2001) Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med* **345:**494–502.

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EXHIBIT D TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

CHAPTER 28

"Daring to be Different": The Discovery of Ticagrelor

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28.1 PROLOGUE

On Christmas Eve 2010, the first pack, anywhere in the world, of a new oral anti-platelet agent, ticagrelor (BRILINTA®, BRILIQUE™), was dispensed in Blackpool. A fitting event for a transformational medicine imagined, designed and initially developed in the UK: a compound that, in the pivotal Phase III study (PLATO)[1] involving more than 18 000 patients, demonstrated that, for every 72 patients with acute coronary syndromes (ACS) treated for 12 months with ticagrelor instead of clopidogrel, one more person gets to live. This case study tries to give some feel for the Discovery story behind ticagrelor. It is a story that spans three decades, so some details are necessarily sketchy, being dependent on the authors' diminishing recall. It is, of course, a story of the science behind ticagrelor but it also illustrates that ground breaking science applied by excellent scientists does not guarantee success in our industry. Without the science there is nothing, but success also requires people and teams with imagination, vision, and persistence to generate a momentum that can withstand organisational change and shifting fashion and priorities. Importantly, success comes from an unwavering focus on why we do what we do—the belief that, if we work on the right things, do the right experiments and make the right judgements, we can make a difference to patients' lives.

This chapter is dedicated to former colleagues at the Charnwood R&D site in Loughborough, Leicestershire through the Fisons, Astra and AstraZeneca years. Be proud of the fact that, at the time of writing, a medicine that came from the innovative "Can Do" Charnwood spirit is, in Leicestershire alone, being used to treat hundreds of patients each year.

28.2 ACUTE CORONARY SYNDROMES (ACS)—A STICKY PROBLEM

In Europe, Brilique, co-administered with acetylsalicylic acid (aspirin, ASA), is indicated for the prevention of atherothrombotic events in adult patients with Acute Coronary Syndromes

The Handbook of Medicinal Chemistry: Principles and Practice
Edited by Andrew Davis and Simon E Ward

Published by the Royal Society of Chemistry, www.rsc.org

(unstable angina, non ST elevation Myocardial Infarction [NSTEMI] or ST elevation Myocardial Infarction [STEMI]); including patients managed medically, and those who are managed with percutaneous coronary intervention (PCI) or coronary artery by-pass grafting (CABG).[2]

ACS represents a life-threatening manifestation of atherosclerosis.[3] It is usually precipitated by acute thrombosis induced by a ruptured or eroded atherosclerotic coronary plaque, with or without concomitant vasoconstriction, causing a sudden and critical reduction in blood flow.

However ACS manifests in a given patient, the underlying acute pathophysiology is driven by the activation and aggregation of platelets in one or more damaged/narrowed coronary arteries, resulting in partial or complete thrombotic occlusion of the artery and intermittent or complete interruption of the blood supply to the heart muscle. Mechanical interventions such as PCI, which involves dilatation of the artery with a balloon catheter and insertion of a stent to maintain vessel patency, reduce the risk of death or myocardial infarction in ACS patients. However, the intervention itself causes considerable disruption and damage to the blood vessel wall that can also lead to thrombotic complications. The pivotal role of platelets in this process has led to the adoption of anti-platelet strategies for both the treatment of ACS and for prevention of the complications of PCI.[3] The main mechanisms that have been targeted are visualised in the simplified schematic of platelet activation and aggregation in Figure 28.1. The cartoon highlights two mechanisms, thromboxane (TxA_2) receptor activation and $P2Y_{12}$ receptor activation (by adenosine diphosphate, ADP), the understanding of which has led to dual anti-platelet therapy with aspirin and an oral $P2Y_{12}$ antagonist becoming the mainstay of anti-platelet therapy in ACS.

Prior to approval of ticagrelor and its inclusion in ACS treatment guidelines, only indirect (pro-drug) oral $P2Y_{12}$ inhibitors were available, and clinical practice guidelines recommended dual anti-platelet treatment with aspirin and clopidogrel. However, the efficacy of clopidogrel is hampered by the slow and variable transformation of the prodrug to the active metabolite,

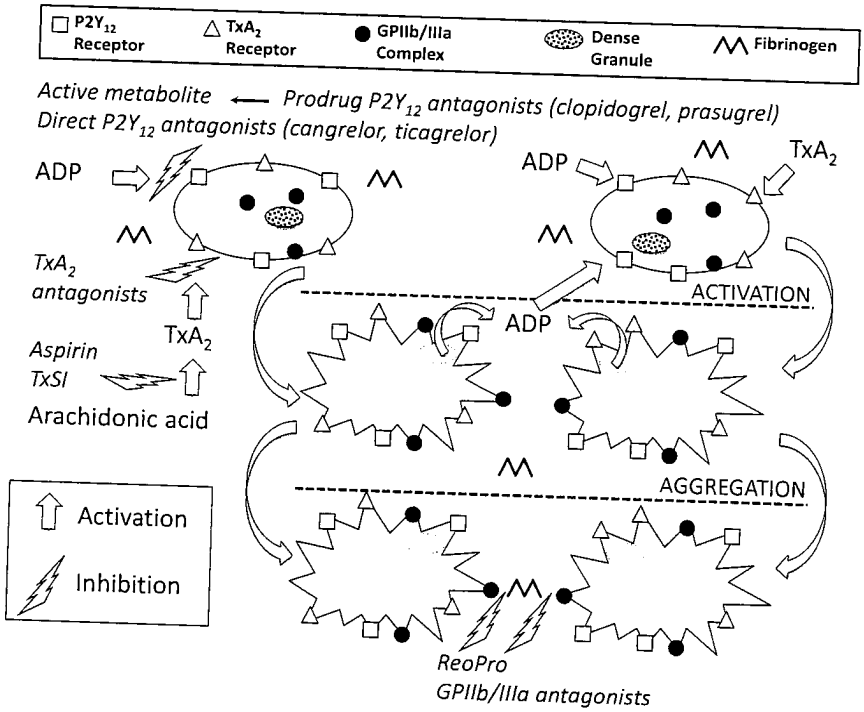

Figure 28.1 Key platelet activation pathways.

modest and variable platelet inhibition, an increased risk of bleeding, and an increased risk of stent thrombosis and myocardial infarction in patients with a poor pharmacodynamic response.[4] As compared with clopidogrel, prasugrel, another thienopyridine prodrug, has a more consistent and pronounced inhibitory effect on platelets, resulting in a lower risk of myocardial infarction and stent thrombosis, but is associated with a higher risk of major bleeding in patients with an acute coronary syndrome who are undergoing percutaneous coronary intervention (PCI).[4] Bleeding risk also reflects the fact that both clopidogrel and prasugrel are irreversible inhibitors of the $P2Y_{12}$ receptor and restoration of normal haemostasis requires generation of new platelets.

Ticagrelor provides a new therapeutic option in ACS as the first direct acting, reversible $P2Y_{12}$ receptor antagonist.[5] In addition, ticagrelor and other potent, selective $P2Y_{12}$ antagonists from the Charnwood $P2Y_{12}$ antagonist project acted as precision pharmacological tools to help explain the relative roles of $P2Y_{12}$ and $P2Y_1$ receptors on platelets,[6] and how targeting the $P2Y_{12}$ receptor can lead to profound clinical benefit.[7] Adenosine diphosphate (ADP), the endogenous agonist at the $P2Y_{12}$ receptor, is an important primary stimulus of sustained platelet activation and is also released from dense granules of platelets activated by ADP or other stimuli.[8–10] Targeting this pathway inhibits platelet activation and, consequently, platelet aggregation, dense and α-granule secretion and further pro-coagulant activity. Thus, the ADP/$P2Y_{12}$ axis plays an important role in amplifying and sustaining platelet activation initiated by other pathways, leading to stable platelet-rich thrombus generation.[11,12] Consequently, blocking the $P2Y_{12}$ receptor has important inhibitory effects on overall platelet function regardless of the initial activating stimuli.[13]

So, with pivotal, definitive clinical studies completed, ticagrelor available to patients, further studies in progress, ADP/$P2Y_{12}$ pharmacology unravelled and the shortcomings of thienopyridines fully understood, it is obvious now that the $P2Y_{12}$ receptor is an excellent therapeutic target—but, how did things look 25 years ago?

28.3 "I WOULDN'T START THERE"

At the start of any long and difficult journey into the unknown there are always plenty of reasons not to take the first step. In the case of ticagrelor, there are a host of reasons why it might never have existed (see Figure 28.2). In the late 1980s, when the story started, there was a surge of interest in anti-platelet therapy for the prevention of thrombotic events. Aspirin had transformed the outlook for patients with coronary artery disease,[14] leading to substantial efforts across the industry to identify alternative, more selective means (thromboxane (TxA2) antagonists, thromboxane synthase inhibitors (TxSI)) of inhibiting generation or effects of products of the cyclooxygenase pathway (see Figure 28.1). The other area pursued by most big Pharma active in the thrombosis field was to develop antagonists of the fibrinogen receptor (the glycoprotein IIb/IIIa complex, GPIIb/IIIa) on platelets, based on the rationale that this approach would deliver maximal anti-platelet efficacy by blocking the final common pathway in platelet aggregation, namely the cross-bridging of individual platelets by fibrinogen to form a platelet rich thrombus.[15,16] Against this background, with aspirin established, TxA_2 antagonists and TxSIs in development, GPIIb/IIIa antagonists emerging, the idea of following another single mediator approach by targeting the $P2Y_{12}$ (known then as P2T) receptor on platelets was, on the face of it, counter-intuitive, particularly since the only chemical starting point was adenosine triphosphate (ATP) for which if asked "where would you start to develop a new drug?" the answer would be "...well, I wouldn't start there." This view was easily compounded by a risk aversion to doing something different rather than follow the logic that, if everyone else is doing something then it must be the right thing—so we should do that too.

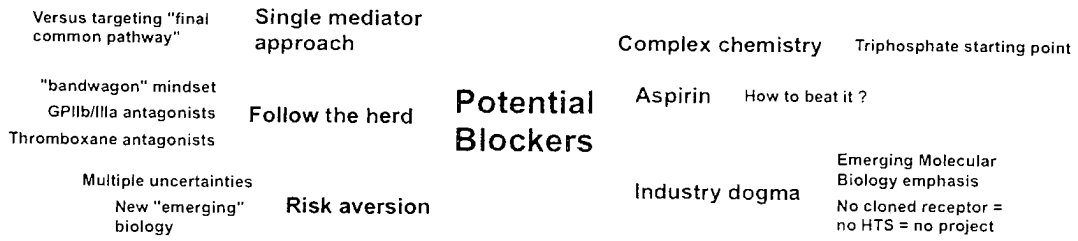

Figure 28.2 Potential blockers (real & perceived) to project initiation.

28.4 "YOU HAVE TO START SOMEWHERE..."—THE ROLE OF CANGRELOR

...and it started in the Fisons Pharmaceuticals research laboratories on the outskirts of Loughborough in the UK, which later became the Charnwood R&D site within AstraZeneca. The geographical location and resultant connections and partnerships are a big part of the ticagrelor success story.

The story started with the coming together in the late 1980s/early 1990s of two areas of research at the Charnwood site. Firstly, a naïve assessment, with no legacy in the platelet field and, therefore, no preconceptions, of where the unmet need for anti-platelet therapy might lie. Here, the geography came into play. Firstly, with the Glenfield hospital cardiology group close by, it was easy to talk to the then Professor of Cardiology, David de Bono, and obtain his insights on what would make a difference for him. At that time, the intravenous inhibitors of the platelet GPIIb/IIIa complex were becoming available for use as adjunctive therapy in coronary artery interventions.[15,16] However, it was also apparent that, with such a mechanism, there was a delicate balance between beneficial effects on thrombosis and increased bleeding risk, particularly when effects were slowly reversible. The second location factor was the proximity to Queens Medical Centre in Nottingham and the invitation to join a Platelet Discussion Group run by Professor Stan Heptinstall. This was to become a long lasting collaboration, later also involving Rob Storey who went on to become Professor of Cardiology at Sheffield and one of the lead investigators in both the cangrelor and ticagrelor clinical programmes.

From these, and other discussions, a target product profile (TPP) was identified requiring an intravenous product with rapid onset of effect, high anti-platelet efficacy and selectivity and rapid offset.

Alongside the unmet need discussions, an assessment of the mechanisms that might provide high anti-platelet efficacy led to a conclusion that blocking platelet aggregation induced by ADP held the most interest. Although, on the face of it, this was another single mediator approach, close scrutiny of the literature provided the clues that ADP could play an important amplifying role in the platelet response to most stimuli, particularly due to its presence and release from storage granules in activated platelets.[10] In addition, this was a period when clinical data were emerging for the thienopyridines ticlopidine, and later clopidogrel.[17] These orally-active compounds inhibit ADP induced platelet aggregation but in an indirect (as prodrugs), irreversible manner and, therefore, did not address the TPP we had identified.

The second area of research was a broad programme aimed at finding novel chemicals (selective receptor agonists/antagonists) to determine the importance of different subtypes of P2 receptors in human disease and to understand the therapeutic opportunities. Without this broad approach it is unlikely that the $P2Y_{12}$ antagonist project would have started—in isolation and with the challenges outlined above it is difficult to see that the substantial Medicinal Chemistry effort required would have been supported. In the event, much of the early chemistry was quite broad to support an overall exploration of the then known subtypes of P2 receptor.

The anti-platelet and P2 receptor themes centred on ADP came together with the knowledge that, while ADP was the endogenous agonist (stimulator) of the $P2Y_{12}$ receptor, uniquely located on platelets, adenosine triphosphate (ATP) was a natural antagonist at this receptor.[18] ATP was, however, a challenging starting point when attempting to design a potent, selective $P2Y_{12}$ antagonist for acute use: some properties (short half-life, high aqueous solubility) were ideally suited for this purpose; other properties (metabolic breakdown to the natural $P2Y_{12}$ agonist (ADP), lack of selectivity versus other P2 receptors) were problematic. However, Medicinal Chemistry and Pharmacological clues were there from work conducted at the Universities of Sheffield[19] and Middlesex[20,21] showing that this natural antagonist could be modified to yield stabilised ATP analogues with selectivity for the $P2Y_{12}$ receptor. Most of the pieces of the jigsaw existed—what the early $P2Y_{12}$ project within Fisons Pharmaceuticals did was to bring these pieces together: unmet medical need; tailored TPP; novel chemistry; integrative pharmacology; a strong Experimental Medicine capability—to design, deliver and develop AR-C69931MX (cangrelor),[22] the first direct acting, reversible intravenous $P2Y_{12}$ antagonist to progress into studies in patients.

Cangrelor is an important potential product in its own right, now under development by The Medicines Company, who specialise in acute care therapies. It is also an important component of the ticagrelor story—cangrelor and related compounds[23,24] removed the biological doubt and proved that targeting a "single mediator" approach could provide a broad spectrum profile. It led to a position where the $P2Y_{12}$ field was largely defined by AstraZeneca compounds, research, publications and collaborations.

So, without cangrelor, ticagrelor would not have existed. Even with the compelling evidence being generated with cangrelor, internal scepticism about being "different" remained; without it the concept of an oral direct acting $P2Y_{12}$ receptor antagonist would not have seen the light of day. In the event, innovative spirit shone through and the journey from cangrelor to ticagrelor started.

28.5 TOWARD TICAGRELOR

A crucial part of the story at this stage was the growing understanding that not all patients respond well to the thienopyridine (indirect) $P2Y_{12}$ antagonists exemplified by clopidogrel.[25] The need for metabolic conversion to an active metabolite introduced a variability not seen with cangrelor and so the concept that a direct acting $P2Y_{12}$ antagonist could fully realise the potential of the $P2Y_{12}$ antagonist mechanism, by providing more complete and consistent inhibition of platelet activation than the thienopyridines, was born. This became a differentiating thread for ticagrelor that linked basic science and preclinical data, through the Phase I and Phase II clinical trials and through, ultimately, to improved clinical outcomes in the PLATO study.

But... to rewind to the start of the oral $P2Y_{12}$ antagonist programme, here, with the pharmacological rationale gaining growing credence, the challenge lay in Medicinal Chemistry and in DMPK—how to move from a molecule such as cangrelor, with properties ideal for its intended clinical use in the acute setting, but completely incompatible with that of an orally active therapy for chronic treatment—to something that could go head-to-head with clopidogrel. This challenge was exacerbated by the fact that, at this time, the $P2Y_{12}$ receptor remained defined only by its function and its pharmacology.[26] The structure of the receptor was not known, and it was yet to be confirmed as a P2Y subtype with the "12" designation. Consequently, no cloned and expressed system (or suitable radioligand) was available to support high throughput screening (the structural identity and cloning of the $P2Y_{12}$ receptor was not published until 2001[27]—2 years after selection of ticagrelor as a candidate drug).

Faced with these challenges it would have been easy to walk away. Instead, the Project Team, strongly supported by Astra research management, maintained confidence and commitment and a belief that we could succeed. Progress was dependent on a relatively low throughput, but highly efficient and informative, functional screen (ADP induced aggregation of human washed platelets) and an empirical, hypothesis-driven synthesis/screening strategy. This approach resulted in quite long periods of small incremental steps interspersed with a handful of quite unanticipated transformational structural alterations. In all, from the inception of activities toward an oral compound to identification of the first potent, orally-bioavailable $P2Y_{12}$ antagonist represented 3 years of effort. Two years later ticagrelor was nominated as a Candidate Drug. Below, this journey is broken down into what, with the benefit of hindsight, can be seen as distinct phases of the story, each enabled by a landmark finding. Outlined for each phase are the key scientific steps taken toward the ultimate goal and highlights of the key themes, learnings and ways of working that enabled success. A common format Figure is provided summarising the following for each phase:

- The key challenge/issues faced.
- The Chemistry strategy pursued.
- The focus of the Biology (Pharmacology/DMPK).
- The key steps forward achieved.

28.5.1 Where to Start?

Where do you start when the starting point is an ATP analogue and the goal is a potent, selective, orally-bioavailable medicine? As mentioned, without access to a high throughput screen, the option of throwing away the template and finding more "druggable" hits was not available. Therefore, the only approach that could be taken was, with cangrelor as the template, to progressively explore whether the main impediments to this goal (high molecular weight, high polarity, multiple charges), and structural features not consistent with or desirable in a molecule for chronic use (adenine ring, glycosidic bond), could be modified or replaced while still retaining potency (Figure 28.3).

The first step recognised that, in cangrelor, an analogue of the endogenous $P2Y_{12}$ antagonist, ATP, the terminal phosphate group was essential for antagonism. The approach taken was, therefore, to find alternative acidic groups which could mimic the polyphosphate chain and particularly the C-phosphate unit of ATP. This initial strategy led to the discovery of a series of aspartic acid-derived di-carboxylic acids. Initially, with retention of the adenine (X = carbon) and ribose (Y = oxygen) rings, the highest attainable potency for inhibition of ADP-induced aggregation of human washed platelets was a pIC_{50} of 7.0, some 300-fold less potent than cangrelor ($pIC_{50} = 9.4$). However, we had completely replaced the triphosphate and achieved $P2Y_{12}$ antagonist potency and selectivity substantially higher than ATP itself ($pIC_{50} = 3.5$). There then followed two of the landmark events of the ticagrelor story: introduction of triazolopyrimidine (X = N) as an isostere of purine and replacement of the ribose oxygen with carbon. These two heroic pieces of medicinal chemistry resulted in a compound with comparable $P2Y_{12}$ antagonist potency ($pIC_{50} = 9.5$) to that of cangrelor but with considerable progression away from the triphosphate starting point, and optimism that further progress could be made. In particular, the triazolo benefit in affinity was seen in all cases and allowed previously impossible changes to be applied. Selectivity amongst P2 receptors was always maintained.

One of the key themes emerging from this phase of the project was that, with the difficulty of the chemistry, it was compound synthesis that was the rate-limiting step and the biology effort could initially be quite streamlined, predominantly focused on the primary assay for $P2Y_{12}$

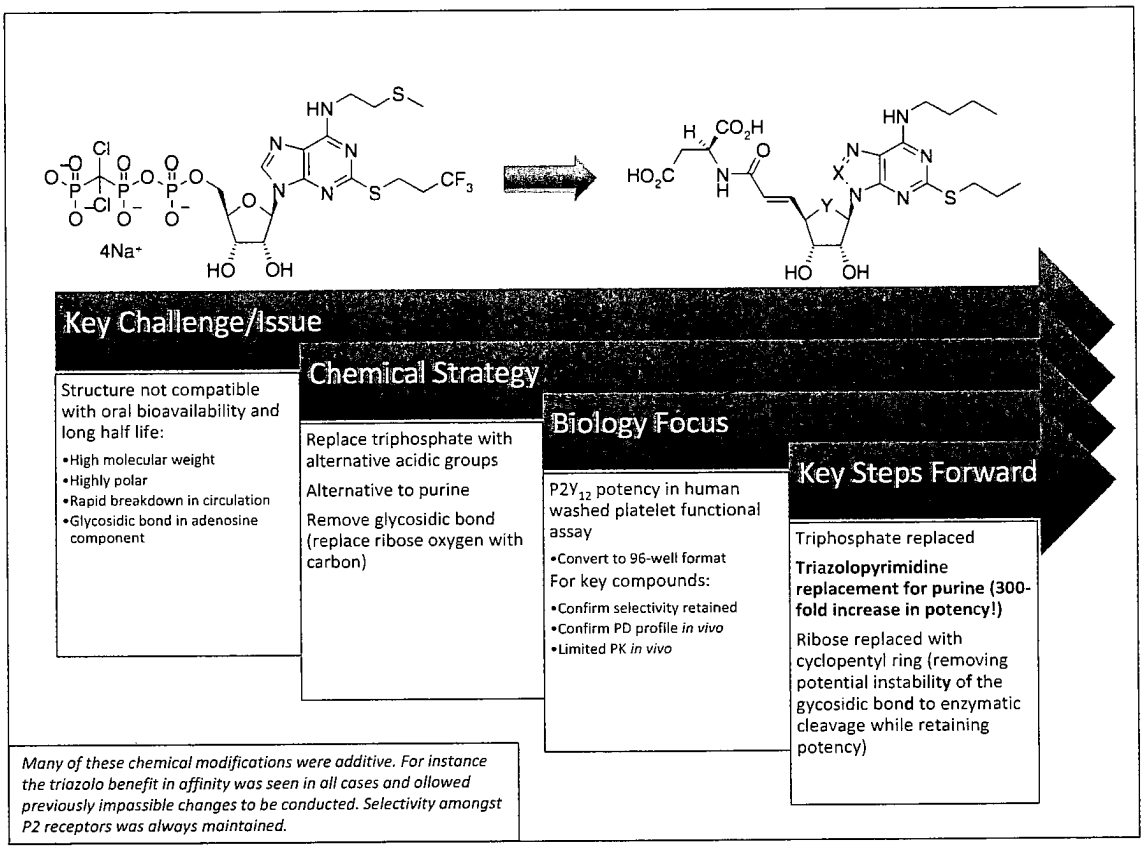

Figure 28.3 Where to start – replacing the triphosphate.

antagonist potency. This allowed the pharmacology team to complete more complex profiling of cangrelor, including building a strong differentiation story *vs.* GPIIb/IIIa antagonists in a dog model of thrombosis.[28] In turn, this built a database and expertise that subsequently helped support the oral $P2Y_{12}$ programme. However, as progress began to be made with achieving the potency goal, three things became apparent: 1) That chemistry output would need to increase if we were to deliver an optimised compound(s) in an acceptable time frame; 2) that this would require a higher capacity primary screen; and 3) that, as we moved toward more "druggable" molecules, we would need to increase capability and capacity for investigating drug metabolism and pharmacokinetics.

28.5.2 Taking Charge

Replacement of the triphosphate and the potency enhancement provided by triazolopyrimidine were encouraging steps. However, it was clear that the di-carboxylic acid compounds, although potent, were subject to rapid biliary clearance and not orally-bioavailable. Clearly, to achieve the project objective, we needed to reduce size, complexity and charge. This was indeed achieved, firstly by moving to mono-carboxylic acids and then with the landmark of achieving $P2Y_{12}$ affinity in a neutral compound (Figure 28.4), with a reasonable pIC_{50} of 7.7. Importantly, this compound was not subject to biliary clearance. Instead, metabolite identification from *in vivo* DMPK experiments indicated that it was subject to hepatic metabolism. This observation moved us significantly closer to the goal of a long acting oral compound since it offered a much higher

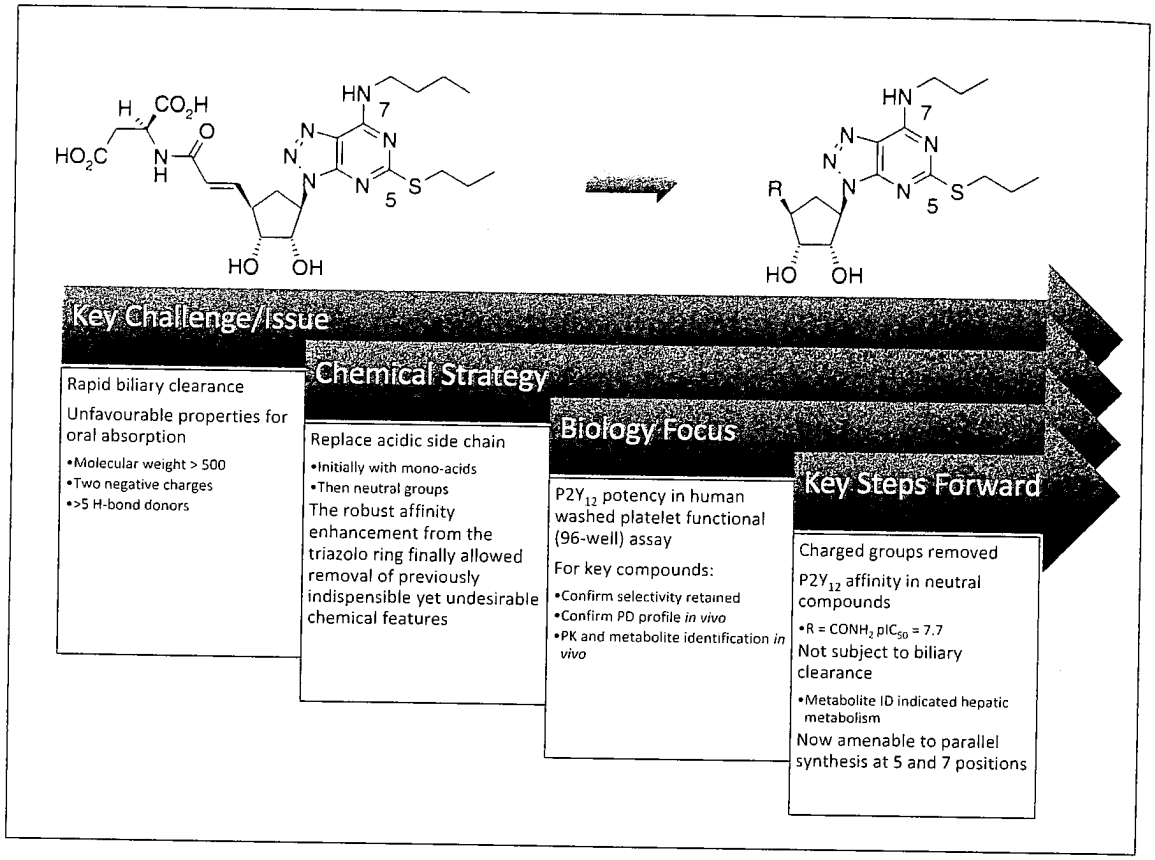

Figure 28.4 Taking charge – affinity and "normal" metabolism in neutral compounds.

likelihood of being able to make PK and dose predictions to man, based on a combination of *in vitro* metabolism data and *in vivo* metabolism and PK studies in the rat and dog.

Importantly, these less complex, neutral molecules now made it possible to increase the medicinal chemistry output, in particular by accessing the then emerging technology of parallel synthesis, enabling multiple reactions and permutations of substituent changes to be conducted in 96-well plates. In turn this was supported by conversion of the primary $P2Y_{12}$ screen to a 96-well format, initially still as a functional assay, but later as a radiolabel displacement assay, requiring identification and synthesis of a novel radioligand and development and validation of the assay. These changes exemplified another theme in the project—the flexibility and ingenuity of the team to continually evolve the key screens to adapt to the changing needs of the project and to access novel technologies, while still maintaining project delivery.

28.5.3 Parallel Universe

At this point in the project great strides had been made and considerable distance achieved from the original triphosphate starting point. However, these first neutral compounds were far from optimised—active yes—but not sufficiently so, and still with many deficits that precluded oral bioavailability and long duration of action (Figure 28.5). Here we encounter another landmark for the project—the identification, through parallel synthesis and the 96-well format primary screen, of the potency-enhancing phenylcyclopropylamine substituent that, importantly, also resulted in the first orally-active compound. This was the breakthrough that

convinced the team that we were very close to candidate drug (CD) quality molecules. The growing understanding of the properties and challenges associated with the core structure also enabled refinement of the criteria required for a compound to be considered as a serious CD contender (Table 28.1).

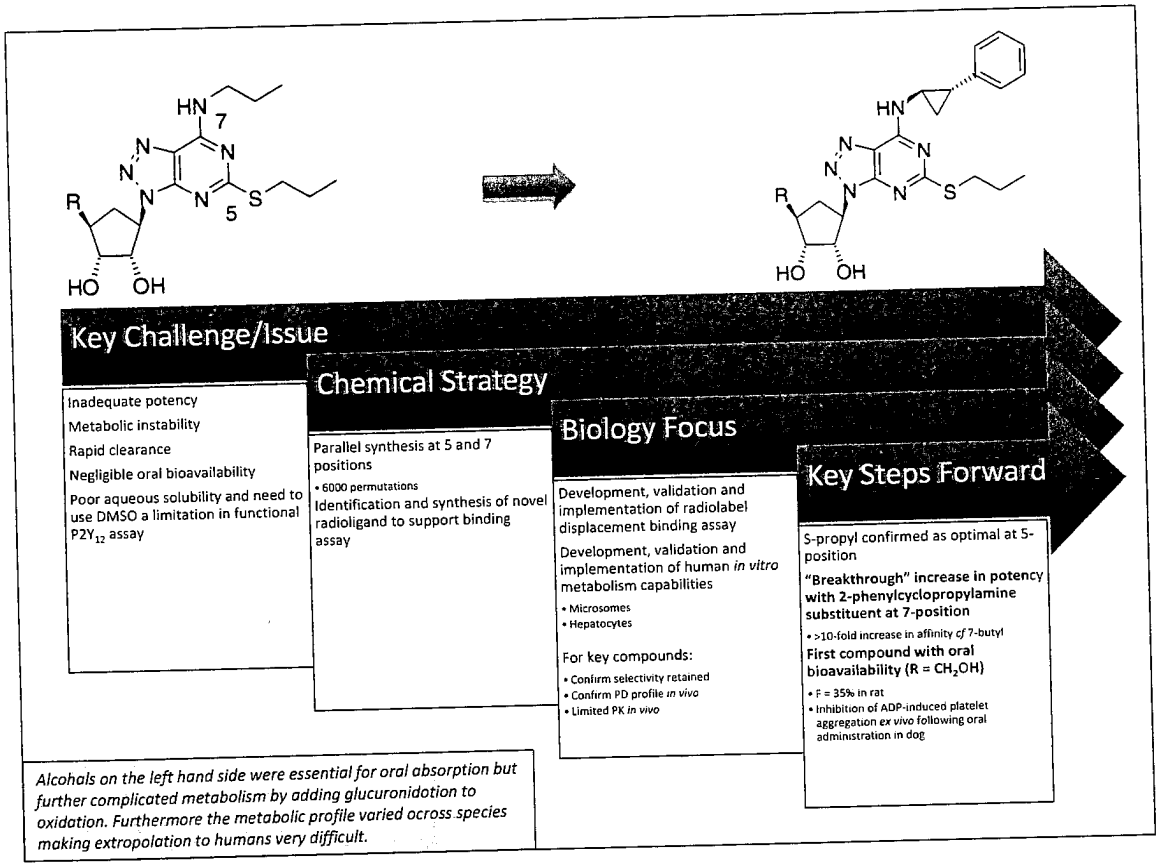

Figure 28.5 Parallel universe – emerging technology leads to unanticipated gain in potency.

Table 28.1 Outline selection criteria during prenomination phase of oral P2Y12 antagonist project.

Attribute	Criterion
Potency	$IC_{50} \leq 10$ nM *vs.* ADP-induced aggregation of human washed platelets *in vitro*. ID_{100} (inhibition of platelet aggregation *ex vivo* in dog) < 2 mg · kg^{-1} po bid.
Selectivity and specificity *in vitro*	At least 100-fold selectivity for the $P2Y_{12}$-receptor over other P2 receptor subtypes and unrelated mechanisms.
Duration	$t_{1/2}$ sufficient to support twice daily dosing in man: exact value dependent on acceptable bleeding time prolongation at predicted plasma C_{max} and interspecies scaling.
Oral bioavailability	$> 30\%$: screening target $> 30\%$ (rat); $> 50\%$ (dog).
Hypothesis testing *in vivo*	Inhibition of ADP-induced platelet aggregation *ex vivo* after oral dosing. Abolition of thrombosis in the anaesthetised dog cyclic flow reduction (CFR) model following intravenous dosing - confirmed with selected CD *via* GI route (intraduodenal).
Therapeutic index	Anti-thrombotic:bleeding time ratio better than GPIIb/IIIa antagonists.

However, there remained another twist in the tale. Namely, that the growing capability in techniques for assessing metabolism *in vitro* in liver microsome preparations and in hepatocytes from rat, dog and human, had identified significant qualitative and quantitative species differences in clearance routes and sites and extent of metabolism, making it difficult to predict, with any degree of certainty, the likely bioavailability, half-life and required dose in man. The major route of clearance in the rat of these lipophilic, neutral compounds was oxidative metabolism whereas clearance was higher as a fraction of hepatic blood flow in the dog and progressed principally *via* glucuronidation. Preliminary data from human hepatocytes suggested that human clearance was also likely to be *via* glucuronidation within the carbocycle. These observations indicated the pivotal role of *in vitro* metabolic screens and the emphasis in particular on robust *in vitro* human data. The DMPK complexities moved the Project into a phase where the predominant structure-activity information driving compound design was human *in vitro* metabolism data. There was little general precedent for this at the time, and the $P2Y_{12}$ antagonist project was the first project within Astra to fully integrate this approach into the synthesis/screening cycle and compound optimisation.

28.5.4 The Human Factor

At this stage, with growing understanding of properties and challenges of the lead compounds, it became apparent that the target profile of any compound suitable for progression would include having a predicted PK/PD profile consistent with twice daily dosing in man at a dose of <0.2 mg/kg. This in part reflected the recognised chemical complexity of the lead compounds and likely cost of goods implications, based on the knowledge available and the assumptions applied at that time. The ability to make predictions of human PK and dose with as much confidence as possible became paramount, and the main focus of the project moved to further optimisation of compounds based on improving metabolic stability in human microsomes and hepatocytes (Figure 28.6). Importantly, fluorination of the aromatic substituent not only reduced the oxidative metabolism. Despite being a remote chemical change, the metabolism on the opposite side of the molecule (glucuronidation of the primary alcohol) was also reduced by this change. This dual effect brought sufficient improvements in metabolic stability for a chronic oral drug to become a reality.

Comparison of intrinsic clearance values obtained in rat hepatocytes and microsomes *in vitro*, with clearance values obtained *in vivo*, provided support for the possibility of predicting the clearance of compounds in man *in vivo* from intrinsic clearance values obtained in human microsomes and hepatocytes *in vitro*. In addition, comparison of anti-aggregatory potency data in dog blood *in vitro* with results from combined PK/PD experiments in the dog *in vivo* supported the use of potency in human blood *in vitro* as a predictor of potency *ex vivo*. This was also supported from clinical data obtained with cangrelor. Using the predicted clearance value *in vivo*, the predicted anti-aggregatory potency (IC_{90}) of the compound in human blood *ex vivo* and other factors, it is then possible (Figure 28.7) to make an estimate of the dose required in man to meet the target profile (12 h full ($\geq$90%) inhibition of ADP-induced platelet aggregation measured *ex vivo*).

The use of the IC_{90} value for inhibition of platelet aggregation in human blood was based on experience in the *in vivo* thrombosis model in the anaesthetised dog that was a key element of the pharmacological profiling of compounds. Developed, validated and refined throughout the course of the project, this complex model allowed a highly integrated assessment of the profile of a compound.[28] Within each experiment, the anti-thrombotic effect was evaluated against dynamic, platelet-mediated thrombosis visualised as cyclic reductions in blood flow (CFR) in the damaged, stenosed femoral artery of the anaesthetised dog. Bleeding time and ADP-induced platelet aggregation *ex vivo* were also measured. The robustness and stability of the model (experiments could be run for up to 12 hours) allowed full dose–response relationships to be

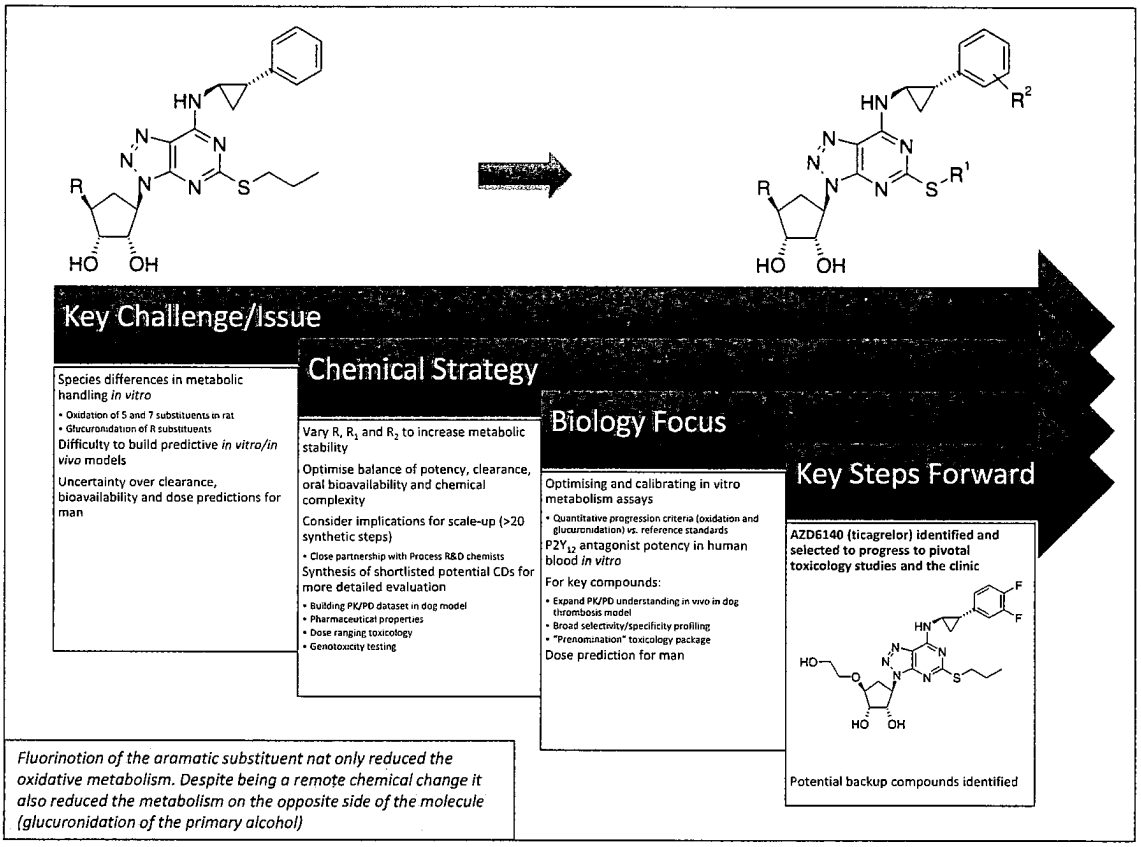

Figure 28.6 The human factor – robust *in vitro* metabolism assays enable human dose prediction.

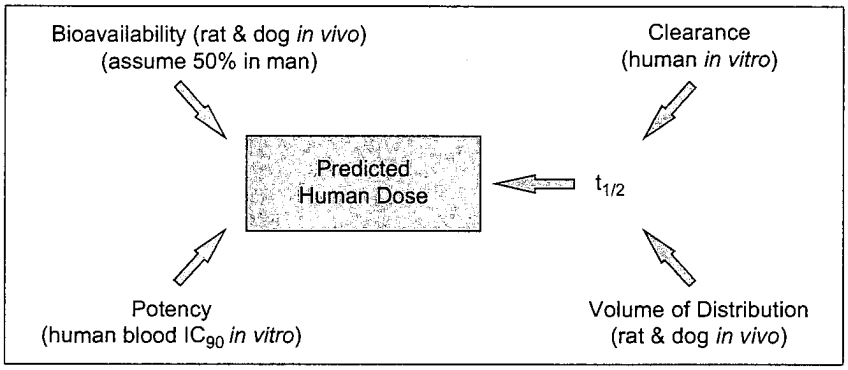

Figure 28.7 Predicting the human dose.

obtained for inhibition of thrombosis, inhibition of platelet aggregation and prolongation of bleeding time. As seen previously with cangrelor, the anti-thrombotic effect of compounds from this phase of the project was achieved with significantly less compromise of haemostasis (bleeding time prolongation) than observed with GPIIb/IIIa antagonists. For all anti-platelet agents tested, regardless of mechanism, complete inhibition of thrombosis required complete/near complete inhibition of platelet aggregation measured *ex vivo*—hence selection of the human blood IC_{90} as a component of the dose prediction.

The model also involved measurement of blood pressure, heart rate, ECG and blood flow in the non-stenosed femoral artery. Therefore, by continuing dose progression above the effective anti-thrombotic dose it was possible to also assess any potential for unwanted cardiovascular effects.

In the early stages of the project, with the focus on achieving potency in new chemical series, and reflecting the chemical complexity, it was usual for the first batch of compound synthesised to be just 10–30 mg. This was appropriate given that many compounds did not progress beyond the primary screen. However, for interesting compounds, this approach could lead to a delay of a few weeks for re-synthesis to support further progression. In the later (prenomination) final optimisation stage of the project, the majority of compounds synthesised were potent, selective, metabolically stable to varying extents, and orally bioavailable. With that in mind, tactics were changed and batch 1 of each compound was made with sufficient quantity to enable data-driven progression from primary screen, through PK and metabolism assessments and to the dog thrombosis model with no delay loop (Figure 28.8). To achieve this rapidly required very close team work and collaboration between all disciplines (medicinal chemistry, analytical and physical chemistry, drug metabolism and pharmacokinetics research, pharmaceutical sciences, pharmacology).

The efficiency that could be achieved is exemplified by experience with a close analogue of ticagrelor for which, from submission of batch 1 of the compound to availability of decision-making data from all the test systems shown took just 1 week.

28.5.5 Complexity of Science, Simplicity of Thought

Since the project was now in a rich vein of compounds and the screening load on these assays and the *in vivo* drug metabolism and pharmacokinetic assessment had become rate-limiting, tough decisions had to be made regarding compound progression. Tough decisions entailed the

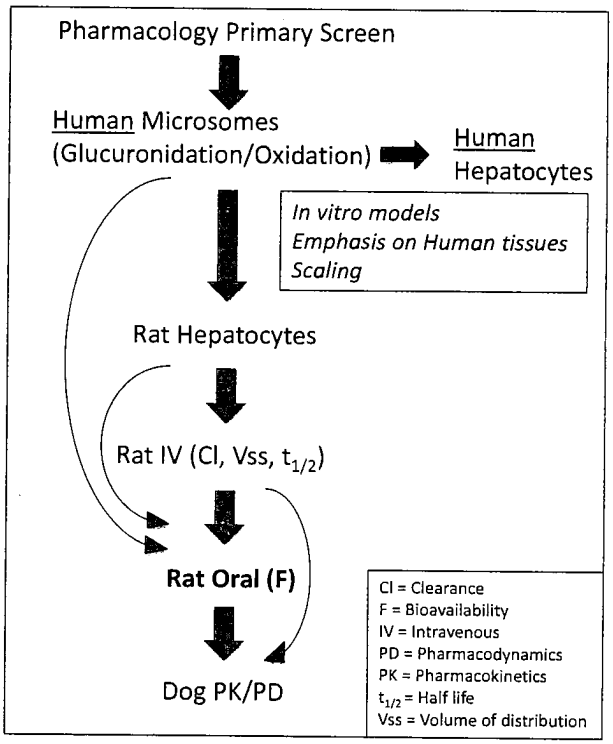

Figure 28.8 Compound progression.

whole project team being comfortable with and jointly owning pragmatic solutions, robust discussions and the making of considered judgement calls on sparse data. Examples of this highly collaborative behaviour included:

- Accepting that, if effort had been put into synthesising a batch 1 quantity sufficient for complete progression, most of the compound would not be used if it failed to progress beyond the primary screen.
- Accepting that we would make decisions to abandon series often on data on just a few representatives if the data indicated a negative trend.
- For many compounds, bypassing the rat intravenous component of progression and moving straight to oral dosing in the rat—if the PK profile after oral dosing was unfavourable that could be a stop decision and we would not necessarily go back to seek the explanation for a poor profile.

So we maintained an unrelenting focus on the ultimate goal of delivering an orally active $P2Y_{12}$ antagonist that could be progressed through safety studies and into the clinic. We only pursued compounds and data that moved the project closer to that goal. All experiments had to support a decision and all other considerations were distractions.

The ultimate achievement was identification of the compound that became ticagrelor.[5]

28.6 BITING THE BULLET

By this stage in the project it was becoming evident that clopidogrel (Plavix) in combination with aspirin would become standard of care in the ACS setting. Commitment to investment in the clinical development programme for ticagrelor would require a high level of confidence that a reversible, direct (non-prodrug) acting $P2Y_{12}$ antagonist would have a differentiated profile compared with clopidogrel. The more rapid onset and offset of effect would provide some advantages but it was clear that clinically-meaningful and reimbursable differentiation would require a significant improvement in efficacy. The scale of the PLATO study (more than 18 000 patients) demonstrates what it would ultimately take to prove this, so how could confidence be built at this early stage, even before the preclinical work to support dosing to man had commenced? The answer lay in the growing body of evidence for "poor responders" to clopidogrel, as assessed by measurement of ADP-induced platelet aggregation measured *ex vivo* following dosing of clopidogrel in healthy subjects or ACS patients. We hypothesised that these patients would remain at a high risk of thrombotic events since their platelets would still be responsive to ADP. An extension of the hypothesis was that if a direct acting $P2Y_{12}$ antagonist were to work pharmacodynamically in all subjects/patients, including those responding poorly to clopidogrel, then, in an appropriately designed and sized clinical study (such as PLATO) there would be a high level of confidence in seeing a significant improvement in efficacy across the study population. Consequently, we conducted a study in which eight healthy volunteers received the standard dose of clopidogrel (75 mg) over a period of 11 days. Blood samples were taken on days 0, 1, 2, 3 and 11. Each blood sample was split and ADP-induced platelet aggregation was measured either in the blood sample as taken or after addition *in vitro* of ticagrelor at its predicted therapeutic concentration. As illustrated in Figure 28.9, following 11 days clopidogrel treatment, in line with other studies, there was substantial variability in the degree of platelet inhibition observed. However, when ticagrelor was "spiked" into the samples, complete/near-complete inhibition was seen, even in blood from the subjects responding poorly to clopidogrel.

This small "translational" study in just eight subjects was prospectively defined as a GO/NO GO study for the project. The result represented a clear GO—we knew that, as long as adequate plasma levels of ticagrelor were achieved, we would see the same pharmacodynamic

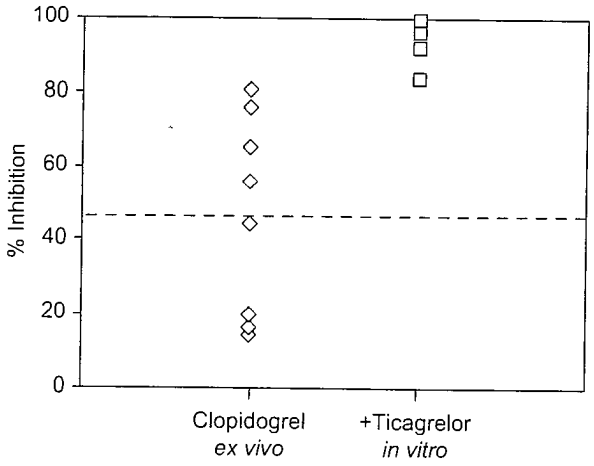

Figure 28.9 Platelet inhibition in blood samples from 8 subjects following 11 days dosing with clopidogrel with and without "spiking" with ticagrelor *in vitro*.

differentiation following oral dosing of ticagrelor in man. This was subsequently confirmed in the Phase I and II clinical development programme.

What about the dose required to achieve this pharmacodynamic effect? How good was the dose to man prediction? The approved dose of ticagrelor (as studied in the PLATO study) is a loading dose of 180 mg (two tablets of 90 mg) followed by 90 mg twice a day for up to 12 months (*i.e.*, a daily dose of 180 mg).[2] The dose prediction at the time of selection of ticagrelor as a candidate drug was 0.2 mg/kg twice daily (14 mg daily dose based on a body weight of 70 kg)—a five- to six-fold underestimate. Contributory factors to this difference are that the dose prediction assumed a bioavailability of 50% (actual bioavailability 36%[2]) and a clearance of <70 mL/min (actual clearance 362–511 mL/min with repeated twice daily dosing[29]). These differences are probably not that surprising, given the human microsome and hepatocyte assays were being developed and validated in parallel with project delivery, the embryonic nature of the science of dose prediction at that time, and the number of assumptions built into the prediction model. Importantly, as discussed in Chapter 8 of this book, information generated from the ticagrelor clinical PK data allowed refinement of the prediction model for subsequent application to other AstraZeneca projects.

28.7 ENABLERS

As discussed above, there were certainly scientific learnings from the $P2Y_{12}$ antagonist project. Perhaps more important though is to reflect on the human factors and ways of working that enabled ultimate success despite all the challenges.

A characteristic of the $P2Y_{12}$ project team was the building of partnerships and ensuring engagement with the wider project team, particularly colleagues who would be inheriting from the Discovery team a compound with significant challenges: complex multistep synthesis; poor solubility; potentially difficult formulation challenges; the need to consider non-standard toxicology species. One of the key factors that enabled seamless progression into early development was recognising those challenges early and building partnerships with the groups that were going to inherit those challenges.

In particular we worked quite differently. We involved Process R&D, Formulation, Toxicology and Experimental Medicine colleagues very early on in the project and they quickly became key members of the extended project team. In particular this enabled the process research and development chemists to make a head start on thinking about alternative routes and scale up.

Throughout the project lifetime, we remained true to our strategic vision and belief—we maintained momentum in the $P2Y_{12}$ antagonist field at a time when it was a difficult area to be working in. Many companies were moving out of novel antiplatelets, with one of the main reasons being that most had invested in the GPIIb/IIIa antagonist class, which, as mentioned previously, target the final common step in platelet aggregation. Targeting that mechanism proved quite successful in the acute hospital settings, with products that are providing benefit to patients. However, many of the orally active compounds with that mechanism advanced into Phase III clinical studies, but failed due to an increase in mortality[30]—for reasons still incompletely understood.

Overlaying all the Project-level factors discussed above was the critical importance of engagement and support at a senior management level. In the Astra years, Research Management had the vision to support initiation of the project, an understanding of complexity, and the patience to give the Team time and space to address complex challenges. Finally, a Phase III study of the scale and cost of PLATO study was a bold recommendation from the ticagrelor Global Product Team, and committing to it a courageous decision by the then leaders of AstraZeneca. As a result, they, and everyone associated with the $P2Y_{12}$ antagonist project, now have the satisfaction of knowing that, by daring to be different, we have been part of delivering a new medicine that, each day, is changing and saving patients' lives.

HINTS AND TIPS—INGREDIENTS FOR SUCCESS

In summary, the scientific and human ingredients for success were:

- Identification of a clear unmet need, patient population and target product profile.
- An unwavering focus on a clearly defined objective.
- Building, applying and translating the scientific knowledge of the mechanism to provide a seamless transition into the clinic using...
- ...a robust, translatable functional assay that allowed progress in the absence of what would typically now be pre-requisites for a project start (cloned receptor, high throughput screen).
- A highly integrated approach, harnessing capabilities in Medicinal Chemistry, Integrative Pharmacology, Experimental Medicine and, crucially, Drug Metabolism.
- Close teamwork enabling rapid decisions to be made, with sparse data, with an unrelenting focus on delivery.
- Building partnerships!
- "Daring to be different" and a "Can Do" attitude.
- Commitment, Courage and Conviction.

KEY REFERENCES

L. Wallentin, R. C. Becker, A. Budaj, C. P. Cannon, H. Emanuelsson, C. Held, J. Horrow, S. Husted, S. James, H. Katus, K. W. Mahaffey, B. M. Scirica, A. Skene, P. G. Steg, R. F. Storey, R. A. Harrington, for the PLATO Investigators, *N. Engl. J. Med.*, 2009, **361**, 1045.

B. Springthorpe, A. Bailey, P. Barton, T. N. Birkinshaw, R. V. Bonnert, R. C. Brown, D. Chapman, J. Dixon, S. D. Guile, R. G. Humphries, S. F. Hunt, F. Ince, A. H. Ingall, I. P. Kirk, P. D. Leeson, P. Leff, R. J. Lewis, B. P. Martin, D. F. McGinnity, M. P. Mortimore, S. W. Paine, G. Pairaudeau, A. Patel, A. J. Rigby, R. J. Riley, B. J. Teobald, W. Tomlinson, P. J. H. Webborn and P. A. Willis, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6013.

R. F. Storey, *Curr. Pharm. Des.*, 2006, **12**, 1255.

REFERENCES

1. L. Wallentin, R. C. Becker, A. Budaj, C. P. Cannon, H. Emanuelsson, C. Held, J. Horrow, S. Husted, S. James, H. Katus, K. W. Mahaffey, B. M. Scirica, A. Skene, P. G. Steg, R. F. Storey and R. A. Harrington, for the PLATO Investigators, *N. Engl. J. Med.*, 2009, **361**, 1045.
2. Ticagrelor Summary of Product Characteristics: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/001241/WC500100494.pdf.
3. C. W. Hamm, J.-P. Bassand, S. Agewall, J. Bax, E. Boersma, H. Bueno, P. Caso, D. Dudek, S. Gielen, K. Huber, M. Ohman, M. C. Petrie, F. Sonntag, M. S. Uva, R. F. Storey, W. Wijns and D. Zahger, *Eur. Heart J.*, 2011, **32**, 2999.
4. L. Bonello, U. S. Tantry, R. Marcucci, R. Blindt, D. J. Angiolillo, R. Becker, D. L. Bhatt, M. Cattaneo, J. P. Collet, T. Cuisset, C. Gachet, G. Montalescot, L. K. Jennings, D. Kereiakes, D. Sibbing, D. Trenk, J. W. Van Werkum, F. Paganelli, M. J. Price, R. Waksman and P. A. Gurbel, *J. Am. Coll. Cardiol.*, 2010, **56**, 919.
5. B. Springthorpe, A. Bailey, P. Barton, T. N. Birkinshaw, R. V. Bonnert, R. C. Brown, D. Chapman, J. Dixon, S. D. Guile, R. G. Humphries, S. F. Hunt, F. Ince, A. H. Ingall, I. P. Kirk, P. D. Leeson, P. Leff, R. J. Lewis, B. P. Martin, D. F. McGinnity, M. P. Mortimore, S. W. Paine, G. Pairaudeau, A. Patel, A. J. Rigby, R. J. Riley, B. J. Teobald, W. Tomlinson, P. J. H. Webborn and P. A. Willis, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6013.
6. G. E. Jarvis, R. G. Humphries and M. J. Robertson, *Leff Br. J. Pharmacol.*, 2000, **129**, 275.
7. R. G. Humphries, *Haematologica*, 2000, **85**, 66.
8. A. Gaarder, J. Jonsen, S. Laland, A. Hellem and P. A. Owren, *Nature*, 1961, **192**, 531.
9. G. V. R. Born, *J. Physiol.*, 1962, **162**, 67P.
10. K. Ugerbil and H. Holmsen, in *Platelets in Biology and Pathology*, ed. J. L. Gordon, Elsevier/North Holland, New York, 1981, Volume 2, p. 147.
11. R. T. Dorsam and S. P. Kunapuli, *J. Clin. Invest.*, 2004, **113**, 340.
12. P. A. Gurbel, K. P. Bliden, K. M. Hayes and U. Tantry, *Expert Rev. Cardiovasc. Ther.*, 2004, **2**, 535.
13. R. F. Storey, *Curr. Pharm. Des.*, 2006, **12**, 1255.
14. Antiplatelet Trialists' Collaboration, *Br. Med. J.*, 1994, **308**, 81.
15. N. S. Cook, G. Kottirsch and H. G. Zerwes, *Drugs Future*, 1994, **19**, 135.
16. T. Weller, L. Alig, M. M. Hürzeler, W. C. Kouns and B. Steiner, *Drugs Future*, 1994, **19**(5), 461.
17. CAPRIE Steering Committee, *Lancet*, 1996, **348**, 1326.
18. D. E. Macfarlane and D. C. B. Mills, *Blood*, 1975, **46**, 309.
19. G. M. Blackburn, D. E. Kent and F. Kolkmann, *J. Chem. Soc. Perkin Trans.*, 1984, **I**, 1119.
20. N. J. Cusack and S. M. O. Hourani, *Br. J. Pharmacol.*, 1982, **76**, 221.
21. N. J. Cusack and S. M. O. Hourani, *Br. J. Pharmacol.*, 1982, **75**, 397.
22. A. H. Ingall and J. Dixon, *J. Med. Chem.*, 1999, **42**, 213.
23. R. G. Humphries, W. Tomlinson, A. H. Ingall, P. A. Cage and P. Leff, *Br. J. Pharmacol.*, 1994, **113**, 1057.
24. R. G. Humphries, W. Tomlinson, J. A. Clegg, A. H. Ingall, N. D. Kindon and P. Leff, *Br. J. Pharmacol.*, 1995, **115**, 1110.
25. B. Boneu, G. Destelle, on behalf of the study group, *Thromb. Haemostasis*, 1996, **76**, 939.
26. J. L. Gordon, *Biochem. J.*, 1986, **233**, 309.
27. G. Hollopeter, H.-M. Jantzen, D. Vincent, G. Li, L. England, V. Ramakrishnan, R.-B. Yang, P. Nurden, A. Nurden, D. Julius and P. B. Conley, *Nature*, 2001, **409**, 202.
28. P. Leff, M. J. Robertson, R. G. Humphries, in *Purinergic Approaches in Experimental Therapeutics*, ed. K. A. Jacobson and M. F. Jarvis, Wiley-Liss Inc, New York, 1997, p. 203.
29. K. Butler and R. Teng, *Br. J. Clin. Pharmacol.*, 2010, **70**, 65.
30. D. P. Chew, D. L. Bhatt, S. Sapp and E. J. Topol, *Circulation*, 2001, **103**, 201.

EXHIBIT E TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/296,990	12/02/2002	Martin Bohlin	3764-129	7436

23117 7590 01/14/2004

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ARLINGTON, VA 22201-4714

EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	6

DATE MAILED: 01/14/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/296,990	BOHLIN ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-32 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-32 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-20, 24, 28-32 are rejected under 35 U.S.C. 102(e) as being anticipated by Harndern 6525060.

See example 3, which prepares the indicated compound. The reference is silent as to the physical form, whether or not is it hydrated, and melting point. Claim 1 and 28 require that the material be substantially crystalline, meaning that it embraces a mixture of crystalline and non-crystalline material, while claim 15 has the opposite, substantially amorphous. Claims 3-14 and 17 require either specific crystalline form, or require a melting point or melting point range, which apparently amounts to about the same thing. Claim 2 has the material in substantially anhydrous form, while claim 16 has the hydrate. Claims 18-20, and 24 use ethyl acetate for the crystallization.

MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the particular crystalline form(s), and the degree of hydration, if any. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is silent on is the crystalline form and degree of hydration.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is. The only difference is a characteristic about which the reference happens to be silent. See also Ex parte Anderson, 21 USPQ 2nd 1241 at 1251, discussion of Rejection E.

Note also that since applicants are claiming both the crystalline and the amorphous forms, one of them must be anticipated. The same is true for hydrous and anhydrous forms. In order to overcome the rejection, applicants need only to replicate

the prior art material and determine its properties. With regard to claims 18-20, and 24, these use ethyl acetate, the same solvent as used by the reference.

Claims 29-32 involve the composition of use thereof. Compositions can be simple solutions in water, and once the material is dissolved, the crystalline form disappears. This can be overcome by limiting the claim to the "solid composition", provided that the claim on which it depends is itself novel.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17, 21-28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

1. The term, "for use ...." in claim 28 simply states an intention, which is a mental step, not a patentable limitation. Hence the claim is improperly dependent, as it does not further limit the claim on which it depends. Alternatively, this may be intended as a method of use claim, in which case, the claim is garbled, as it begins as a compound claim, and ends as a method claim.
2. Claim 17, 21, 23-25, and 27 are unclear as "defined above" has no clear antecedent. Above what?
3. Process claims 21-25, 27 are incomplete because they lack any actual step.
4. The term "formula (1)" in claim 26 should be Formula (I).

5. The term "substantially" in claims 1 and 15 is unclear. Terms of degree, such as "substantial" or "relatively" are indefinite when the specification contains no "explicit guidelines" to distinguish from things which are not so, *Ex parte Oetiker*, 23 USPQ2d 1651, 1655 (1990) and *Ex parte Oetiker*, 23 USPQ2d 1641, and *Seattle Box Co. v. Industrial Crating & Packaging, Inc.* 221 USPQ 568, 574. See also *Ex Parte Anderson*, 21 USPQ2d 1241 at 1250, for "comparable" and "superior". See MPEP 2173.05(b) which states, "When a term of degree is presented in a claim, first a determination is to be made as to whether the specification provides some standard for measuring that degree. If it does not, a determination is made as to whether one of ordinary skill in the art, in view of the prior art and the status of the art, would be nevertheless reasonably apprised of the scope of the invention. Even if the specification uses the same term of degree as in the claim, a rejection may be proper if the scope of the term is not understood when read in light of the specification ... when the scope of the claim is unclear a rejection under 35 U.S.C. 112, second paragraph is proper. See In re Wiggins, 488 F. 2d 538, 541, 179 USPQ 421, 423 (CCPA 1973)."

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 703-308-4718. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on 308-4716. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 708-308-1235.

Mark L. Berch
Primary Examiner
Art Unit 1624

1/12/04

EXHIBIT F TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOHLIN ET AL — Atty. Ref.: 3764-129; Confirmation No. 7436

Appl. No. 10/296,990 — TC/A.U. 1624

Filed: December 2, 2002 — Examiner: Mark L. Berch

For: NEW CRYSTALLINE AND AMORPHOUS FORM OF A TRIAZOLO(4,5-D)PYRIMIDINE COMPOUND

* * * * * * * * * * * *

July 14, 2004

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT

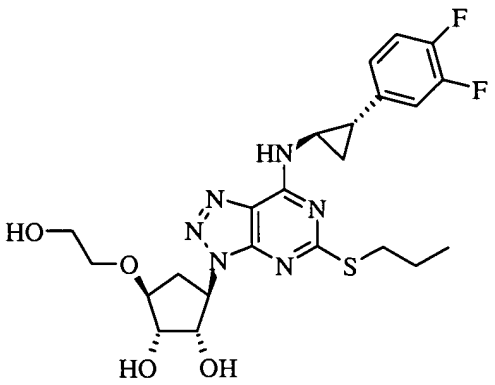
In response to the Official Action mailed January 14, 2004 (for which petition is hereby made for a three-month extension of time), please amend the above-identified application as follows:

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-32 (cancelled).

33 (new). A compound of formula (I):



(I)

in a crystalline form selected from:

a compound of formula (I) characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 5.3° (±0.1°), 20.1° (±0.1°), 20.7° (±0.1°), 21.0° (±0.1°) and 21.3° (±0.1°) 2θ;

a compound of formula (I) characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 14.0° (±0.1°), 17.4° (±0.1°), 18.4° (±0.1°), 21.4° (±0.1°) and 24.1°(±0.1°) 2θ; and

a compound of formula (I) characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 4.9° (±0.1°), 9.2° (±0.1°), 11.6° (±0.1°), 15.6° (±0.1°) and 16.4° (±0.1°) 2θ.

34 (new). A compound of formula (I) as claimed in claim 33 that exists in an anhydrous form.

35 (new). A compound of formula (I) as claimed in claim 33 characterised by an X-ray powder diffraction pattern containing specific peaks at 5.3° (±0.1°), 8.0° (±0.1º), 9.6° (±0.1°), 13.9° (±0.1°), 15.3° (±0.1°), 20.1° (±0.1°), 20.7° (±0.1°), 21.0° (±0.1º), 21.3° (±0.1°), 26.2° (±0.1°) and 27.5° (±0.1°) 2θ.

36 (new). A compound of formula (I) as claimed in claim 33 characterised by a differential scanning calorimetry curve to have an onset of melting which is in the range 146 - 152°C.

37 (new). A compound of formula (I) as claimed in claim 33 characterised by an X-ray powder diffraction pattern containing specific peaks at 5.6° (±0.1°), 12.5° (±0.1°), 14.0° (±0.1°), 17.4° (±0.1°), 18.4° (±0.1°), 21.4° (±0.1°), 22.2° (±0.1°), 22.9° (±0.1°), 24.1° (±0.1°) and 24.5° (±0.1°) 2θ.

38 (new). A compound of formula (I) as claimed in claim 33 characterised by a differential scanning calorimetry curve to have an onset of melting which is in the range 127-132°C.

39 (new). A compound of formula (I) as claimed in claim 33 characterised by an X-ray powder diffraction pattern containing specific peaks at 4.9° (±0.1°), 6.0° (±0.1°), 9.2° (±0.1°), 11.6° (±0.1°), 12.8° (±0.1°), 15.6° (±0.1°), 16.4° (±0.1°), 17.2° (±0.1°) and 18.1° (±0.1°) 2θ.

40 (new). A compound of formula (I) as claimed in claim 33 characterised by a differential scanning calorimetry curve to have an onset of melting which at approximately 139°C.

41 (new). A compound of formula (I) as claimed in claim 33 which is in the form of a hydrate.

42 (new). A process for the preparation of a compound as claimed in claim 33, comprising crystallizing a compound of formula (I) from a solvent selected from the group consisting of a lower alkyl acetate, a lower alkyl alcohol, an aliphatic hydrocarbon, an aromatic hydrocarbon, a dialkyl ether, a dialkyl ketone, acetonitrile, water, and a mixture thereof.

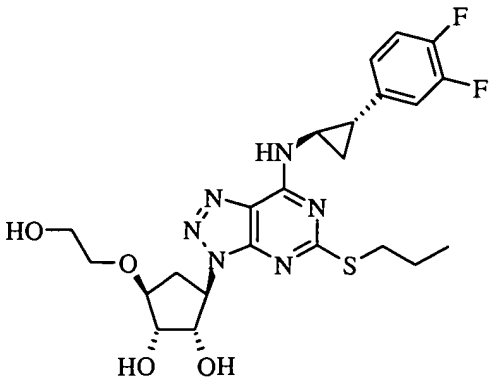
43 (new). A process as claimed in claim 42, wherein the solvent is selected from the group consisting of ethanol, ethyl acetate, *iso*-propanol, *iso*-octane, acetonitrile, water, and a mixture thereof.

44 (new). A process as claimed in claim 43 wherein the solvent is selected from the group consisting of a mixture of methanol and water, ethanol, ethyl acetate, a mixture of ethanol and water, a mixture of *iso*-propanol and water, a mixture of ethyl acetate and *iso*-octane, and acetonitrile.

45 (new). A process for the production of a compound of formula (I) as claimed in claim 33, characterised by an X-ray powder diffraction pattern containing specific peaks at 5.3° (±0.1°), 20.1° (±0.1°), 20.7° (±0.1°), 21.0° (±0.1°) and 21.3° (±0.1°) 2θ, comprising crystallizing the compound of formula (I) from a mixture of methanol and water.

46 (new). A process as claimed in claim 45 which includes the step of using a seed.

47 (new). A process according to claim 46 in which the seed is prepared by melting a compound of formula (I):



(I)

characterized by an X-ray powder diffraction pattern containing specific peaks of high intensity at 5.3° (±0.1°), 8.0° (±0.1º), 9.6° (±0.1°), 13.9° (±0.1°), 15.3° (±0.1°), 20.1° (±0.1°), 20.7° (±0.1°), 21.0° (±0.1º), 21.3° (±0.1°), 26.2° (±0.1°) and 27.5° (±0.1°) 2θ.

48 (new). A process for the production of a compound of formula (I) as claimed in claim 33, characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 14.0° (±0.1°), 17.4°(±0.1°), 18.4° (±0.1°), 21.4° (±0.1°) and 24.1°(±0.1°) 2θ, comprising crystallizing the compound of formula (I) from an alcohol.

49 (new). A process for the production of a compound of formula (I) as claimed in claim 33, characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 14.0° (±0.1°), 17.4°(±0.1°), 18.4° (±0.1°), 21.4° (±0.1°) and 24.1°(±0.1°) 2θ, comprising slurrying a compound of formula (I) in an IPA/water solvent system at a temperature of 5 to 65°C.

50 (new). A process for the production of a compound of formula (I) as claimed in claim 33, characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 4.9° (±0.1°), 9.2° (±0.1°), 11.6° (±0.1°), 15.6° (±0.1°) and 16.4° (±0.1°) 2θ, comprising crystallizing the compound of formula (I) from acetonitrile.

51 (new). A pharmaceutical composition comprising a compound as claimed in claim 33 in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

52 (new). A method of treatment or prevention of arterial thrombotic complications in patients with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound as claimed in claim 33.

53 (new). A method of treatment or prevention of arterial thrombotic complications in patients with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound as claimed in claim 35.

54 (new). A method of treatment or prevention of arterial thrombotic complications in patients with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound as claimed in claim 37.

55 (new). A method of treatment or prevention of arterial thrombotic complications in patients with coronary artery, cerebrovascular or peripheral vascular

disease, which comprises administering to a person suffering from or susceptible to such a disorder a therapeutically effective amount of a compound as claimed in claim 39.

REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 33-55 are in the case.

I. THE ANTICIPATION REJECTION

Claims 1-20, 24, 28-32 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,525,060. That rejection is respectfully traversed.

In response, and without conceding to the merit of the rejection, all of the claims in this application have been cancelled without prejudice and replaced by new claims 33-55. These claims are focused on polymorphs I, III and IV. The cited prior patent does not disclose (or suggest) any of these polymorphs or their preparation.

Withdrawal of the outstanding anticipation rejection is now believed to be in order. Such action is respectfully requested.

II. THE 35 U.S.C. §112, SECOND PARAGRAPH, REJECTION

Claims 17 and 21-28 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for the reasons detailed on pages 4 and 5 of the Action. In response, the new claims presented herewith have been prepared taking into account the Examiner's formal points. The following comments are offered.

The language "for use..." does not appear in any of the claims presented herewith. Withdrawal of that aspect of the formal rejection is respectfully requested.

The claims presented herewith do not include the language "defined above". Withdrawal of that aspect of the rejection is therefore respectfully requested.

The process claims are now recited with a process step. Withdrawal of the objection to claims 21-25 and 27 is therefore respectfully requested.

The minor formal matter referred to in paragraph 4 on page 4 of the Action has received attention. Withdrawal of this aspect of the formal rejection is respectfully requested.

The term "substantially" does not appear in the new claims presented herewith. Withdrawal of the formal point raised in paragraph 5 on page 5 of the Action is respectfully requested.

Allowance of the application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

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EXHIBIT G TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

14)

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/296,990	12/02/2002	Martin Bohlin	3764-129	7436

23117 7590 09/02/2004

NIXON & VANDERHYE, PC
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EXAMINER	
BERCH, MARK L	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/296,990	BOHLIN ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 July 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-55* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *33-44 and 51-55* is/are rejected.

7)☒ Claim(s) *45-50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 33-44 and 51-55 are rejected under 35 U.S.C. 102(e) as being anticipated by Harndern 6525060.

See example 3, which prepares the indicated compound. The reference is silent as to the physical form, or whether it is a hydrate. Claim 33 is drawn to three specific crystalline forms, and the dependent claims, except 41, describe these three forms in more detail. Claim 41 has the hydrate. Process claims 42-44 permit the use ethyl acetate (the solvent used in the reference) for the crystallization. Claim 51 is drawn to the composition of use thereof. Compositions can be simple solutions in water, and once the material is dissolved, the crystalline form disappears, and thus the identical solution is obtained regardless of which crystalline form one began with. Claims 52-55 are drawn to a method which is embracive of what the reference teaches. For example, the last claim of the reference recites stroke, which would fall within the claim language of claims 52-55.

MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY 3

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the particular crystalline form(s), and the degree of hydration, if any. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is silent on is the crystalline form and degree of hydration.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is. The only difference is a characteristic about which the reference happens to be silent. See also Ex parte Anderson, 21 USPQ 2nd 1241 at 1251, discussion of Rejection E.

Note also that since applicants are claiming both the crystalline and the amorphous forms, one of them must be anticipated. The same is true for hydrous and

anhydrous forms. In order to overcome the rejection, applicants need only to replicate the prior art material and determine its properties. With regard to claims 18-20, and 24, these use ethyl acetate, the same solvent as used by the reference.

The traverse is unpersuasive. It does not address the reasoning actually presented in the rejection. Note that these same crystalline forms in e.g. claims 3, 9 and 12 are now just recited in a single claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 41 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 41 does not make sense. Claim 33 sets forth 3 specific crystalline forms, i.e. I, III and IV. The specification states specifically that these are anhydrous forms. An anhydrous compound cannot be in the form of a hydrate.

Claims 52-55 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to

which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim language is so broad that it cannot possibly be enabled. The specification sets forth examples of this as follows: "Arterial thrombotic complications may include unstable angina, primary arterial thrombotic complications of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, including coronary angioplasty (PTCA), endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including ski and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation in vivo, such as cardiopulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation in vitro, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory

bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process." The examiner notes however, that asthma is not normally considered an arterial thrombotic problem. Further, this list just covers disorders where there is too much coagulation. There are still other disorders where a thrombus would be needed but does not form (e.g. hemophilia), which would also fall within these claims, since the claim language is broad enough to cover both categories. Further, these claims cover prevention. Even disorders which can be treated often cannot be prevented. For example, there is no such thing as pharmaceutical prevention of Peripheral vascular disease, myeloproliferative disease, adult respiratory distress syndrome, to name just three. Such a scope thus cannot possibly be deemed enabled.

Claim Objections

Claims 45-50 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

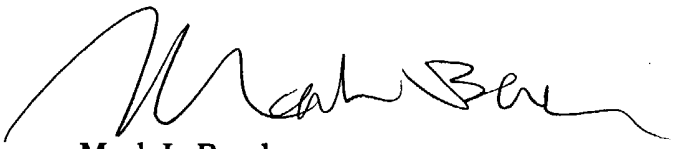
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within

TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mukund Shah can be reached on (571)272-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.



Mark L. Berch
Primary Examiner
Art Unit 1624

8/24/04

EXHIBIT H TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 56-84 are presented for examination.

Attached is a declaration executed by Dr. Steve Cosgrove, a co-applicant of the present application, with attached copies of pages from his laboratory note book dated prior to March 8, 2000 (the U.S. filing date of commonly assigned U.S. patent 6,525,060 to Hardern et al.). The pages record Differential Scanning Calorimetry (DSC) and X-Ray Powder Diffraction (XRPD) experiments and results carried out by Dr. Cosgrove (or under his supervision and control) with respect to the isolation and characterization of Polymorphs I-IV (identified in the attached Note book pages as Forms I-IV), described in the present application.

Page 90 attached to the Cosgrove declaration describes a preparation of Polymorph I, and the page immediately following depicts the X-ray diffraction pattern for Polymorph I (the graph identified as "Form I"). Graphs for Polymorph II (the graph identified as "Form II"), a mixture of Polymorphs II and III (the graph identified as "Form II and III") and Polymorph IV (the graph identified as "ex acetonitrile") are also depicted on this page.

Page 43 describes the recrystallization solvent used to obtain Polymorph II (in respect to compound "AR-C126532XX") and its characterization by powder X-ray diffraction analysis, as depicted by the X-ray diffraction pattern for Polymorph II (the graph identified as "Form II") on the preceding page. Page 89 and continued on page 101 describes a preparation of Polymorph III, and the page immediately following depicts the X-ray diffraction pattern of Polymorph III (the graph identified as "slurried in

acetonitrile" and signed). The two other graphs, top and middle, are also Polymorph III, but are poorer data.

Page 87 reports a preparation of Polymorph IV and depicts the X-ray diffraction pattern for Polymorph IV (the graph identified as "ex acetonitrile"). Graphs for Polymorph II (the graph identified as "Form II"), a mixture of Polymorphs II and III (the graph identified as "Form II and III") and Polymorph I (the graph identified as "Form I") are also depicted on this page.

The X-ray-patterns for Polymorph III on the page following page 101 of the attachment and for Polymorph IV on page 87 are reproduced as Figures 1.3 and 1.4 respectively in the present application. Patterns shown in Figures 1.1 and 1.2 of the present application are similar to but not exactly the same as those shown for "Form I" and "Form II" on page 87, as the measurements which gave rise to the patterns shown in Figures 1.1 and 1.2 of the application were taken at a different time (prior to March 8, 2000).

Page 45 reports that the DSC experiments establish that Polymorph I melts at 151°C., Polymorph II melts at 138°C. and Polymorph III melts at 131°C. Page 87 establishes Polymorph IV melts at 139 °C.

The evidence presented in the attached copies of Dr. Cosgrove's' laboratory note book pages establishes that Polymorphs I-IV were isolated and characterized by X-ray diffraction prior to March 8, 2000. Based on this, it is believed that U.S. patent 6,525,060 is not prior art against the present application.

Favorable action is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
Leonard C. Mitchard
Reg. No. 29,009

LCM:lfm
1100 North Glebe Road, 8th Floor
Arlington, VA 22201-4714
Telephone: (703) 816-4000
Facsimile: (703) 816-4100
Attachment: Cosgrove declaration and attachments

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOHLIN ET AL — Atty. Ref.: 3764-129; Confirmation No. 7436

Appl. No. 10/296,990 — TC/A.U. 1624

Filed: December 2, 2002 — Examiner: Mark L. Berch

For: NEW CRYSTALLINE AND AMORPHOUS FORM OF A TRIAZOLO(4,5-D)PYRIMIDINE COMPOUND

* * * * * * * * * * * *

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION

I, Steve Cosgrove, do hereby declare and state as follows:

1. I am a co-applicant of the present application.

2. I am aware of U.S. patent 6,525,060 to Hardern et al. filed in the United States on March 8, 2000, and commonly assigned with the present application.

3. Attached are true copies of pages from my laboratory note book, all signed by myself and independently witnessed prior to March 8, 2000 (with the dates blanked out), which record Differential Scanning Calorimetry (DSC) and X-Ray Powder Diffraction (XRPD) experiments and results carried out by myself (or under my supervision and control) with respect to the isolation and characterization of Polymorphs

I-IV (identified in the attached Note book pages as Forms I-IV), described in the present application.

4. Page 90 describes a preparation of Polymorph I, and the page immediately following depicts the X-ray diffraction pattern for Polymorph I (the graph identified as "Form I"). Graphs for Polymorph II (the graph identified as "Form II"), a mixture of Polymorphs II and III (the graph identified as "Form II and III") and Polymorph IV (the graph identified as "ex acetonitrile") are also depicted on this page.

5. Page 43 describes the recrystallization solvent used to obtain Polymorph II (in respect to compound "AR-C126532XX") and its characterization by powder X-ray diffraction analysis, as depicted by the X-ray diffraction pattern for Polymorph II (the graph identified as "Form II") on the preceding page.

6. Page 89 and continued on page 101 describes a preparation of Polymorph III, and the page immediately following depicts the X-ray diffraction pattern of Polymorph III (the graph identified as "slurried in acetonitrile" and signed). The two other graphs, top and middle, are also Polymorph III, but are poorer data.

7. Page 87 reports a preparation of Polymorph IV and depicts the X-ray diffraction pattern for Polymorph IV (the graph identified as "ex acetonitrile"). Graphs for Polymorph II (the graph identified as "Form II"), a mixture of Polymorphs II and III (the graph identified as "Form II and III") and Polymorph I (the graph identified as "Form I") are also depicted on this page.

8. The X-ray-patterns for Polymorph III on the page following page 101 of the attachment and for Polymorph IV on page 87 are reproduced as Figures 1.3 and 1.4 respectively in the present application. Patterns shown in Figures 1.1 and 1.2 of the

present application are similar to but not exactly the same as those shown for "Form I" and "Form II" on page 87, as the measurements which gave rise to the patterns shown in Figures 1.1 and 1.2 of the application were taken at a different time (prior to March 8, 2000).

9. Page 45 reports that the DSC experiments establish that Polymorph I melts at 151°C., Polymorph II melts at 138°C. and Polymorph III melts at 131°C, whilst page 87 establishes Polymorph IV melts at 139 °C.

10. The evidence presented in the attached copies of my laboratory note book pages shows that Polymorphs I-IV were isolated and characterized by X-ray diffraction prior to March 8, 2000.

I declare that all statements herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

S. Cosgrove

Steve Cosgrove

26/9/05

Date

Attachments: Laboratory note book pages

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PXRD of Form I of AR-C126532XX

Method. Form I was prepared from the melt of Form II (batch 7) using cycled DSC (method as for PS/149/48 but omitting final ramp to 165 °C). The powder was then placed on a silicon filled sample holder and data collected over 36 hours. Very few peaks could be distinguished between 30 and 70°.

Result. The PXRD (sc) pattern differed from those obtained before, for samples recrystallised from ethyl acetate (Form II pure) and ethanol (Form II and Form III mixed). It is unclear as to whether the PXRD pattern collected here (also sc) contains peaks associated with Form II or Form III ie. whether the sample is mixed Form I with another form. However that the DSC does not indicate any thermal events near the melting points of Form II and III, it seems probable that the PXRD pattern collected here corresponds to pure Form I.

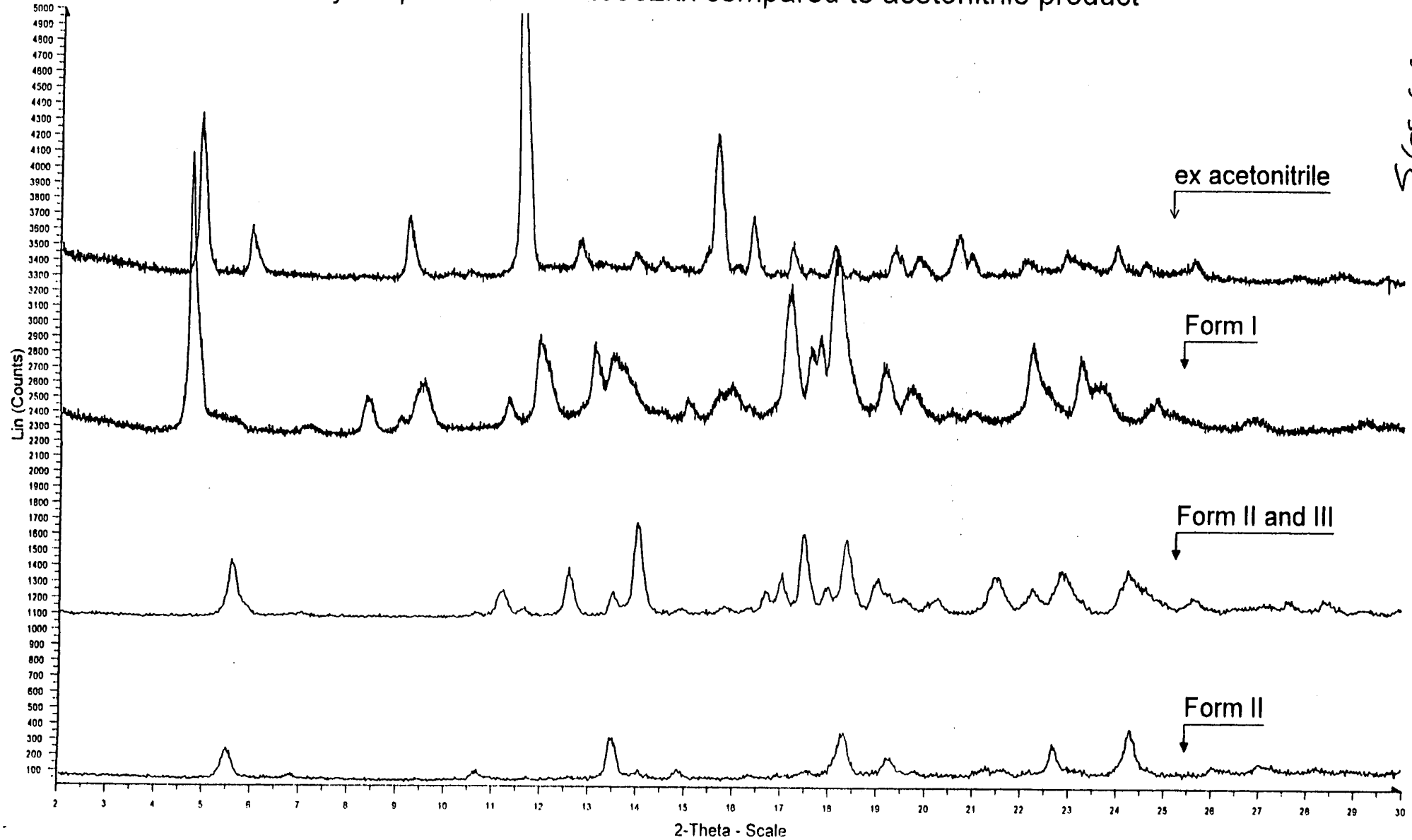
Files: 532Form1.raw - PXRD
5326?Form1 to xid.dsd - DSC

Slurrying-

2-3 drops of a solution of 20% IPA, 80% water were added to the sample whilst it was still on the silicon filled PXRD sample holder. The sample was dispersed using a spatula. The holder was then placed in a petri-dish and sealed with Parafilm, thus preventing the slurry from evaporating. After 15 hours the PXRD was recorded,

S. Cosgrove D. Patel 45

Polymorphs of AR-C126532xx compared to acetonitrile product



AR-C126532xx recrystallised from EtOAc - File: 532etoac.RAW - Type: 2Th/Th locked - Start: 2.000 ° - End: 30.000 ° - Step: 0.020 ° - Step time: 2.0 s - Temp.: Room - Time Started: 9 s - 2
Operations: Import

Y + 30.0 mm - AR-C126532xx recrystallised from EtOH - File: 532etoh.RAW - Type: 2Th/Th locked - Start: 2.000 ° - End: 30.000 ° - Step: 0.020 ° - Step time: 2.0 s - Temp.: Room - Time St
Operations: Import

Y + 60.0 mm - ar-c126532XX annealed to form I - File: Oral P2T532FormI.RAW - Type: 2Th/Th locked - Start: 2.000 ° - End: 70.000 ° - Step: 0.005 ° - Step time: 10.0 s - Temp.: Room - Ti
Operations: Import

Y + 90.0 mm - ar-c126532 recryst acetonitrile PS149/87 - File: 532acetonitrile.RAW - Type: 2Th/Th locked - Start: 2.000 ° - End: 30.000 ° - Step: 0.005 ° - Step time: 10.0 s - Temp.: Room -
Operations: Import

Recrystallisation from EtOH, EtOAc, THF

Samples of AR-C125917XX, AR-C126583XX and AR-C126532XX were recrystallised by David Ennis, PR&D using EtOH, EtOAc, THF, MeOH and Acetone. The yields obtained were as follows:

2434/035/1	EtOH	AR-C126533XX	60%
2434/037/1	EtOAc	"	75%
2434/039/1	THF	"	0%
2434/041/1	Acetone	"	0
2434/043/1	EtOH	AR-C126532XX	85%
2434/045/1	EtOAc	"	90%
2434/047/1	MeOH	"	0%
2434/051/1	EtOH	AR-C125917XX	88%
2434/053/1	EtOAc	"	83%
2434/055/1	THF	"	55%

PXRD

Figure 1 indicates that PXRDs of the recrystallised 917 and 583 samples remain the same structure independent of the solvent used. The sample AR-C126532XX recrystallised from EtOAc showed the same PXRD as ~~those~~ med chem batches ie. no change in polymorphism ≠ Recrystallisation from EtOH results in additional peaks, indicating a mixed phase. ✓

These results are in agreement with DSC of the samples (Page 30 of PS149).

≠ This polymorph is defined as polymorph II, S. Cosgrove in terms of its XRPD.

S. Cosgrove

PS149/23

Ethanol product (Mixed Forms)

44mg Batch 6M (ie micronised) was placed in a vial. To this, 400µl of ethanol was added, and the resulting slurry warmed to dissolution. The mixture had not crystallised by the morning and so flowing N_2 was applied. Unfortunately, the EtOH evaporated quicker (and completely) than expected.

DSC and XRPD were performed prior to slurrying - filenames 532etohlongslu.d
532_149_89.raw

The DSC indicates the ~~pr~~ melting endotherms of 3 polymorphs of AR-C126532XX.

°C		
onset	peak	ΔH
~~x~~ —	133.9	-
135.5	138.2	-
150.3	152.7	3.3J/g

After slurrying, 3 endothermic events again are observed. The highest temperature endotherm, remains essentially unchanged. There appears to be a slight shift of the middle endotherm and a larger shift of the lowest temperature endothermic peak.

°C, H_2O:	onset	peak	ΔH
	123.6	130.5	-
	134.1	137.1	-
	151.0	152.8	1.9

See Page 101 for continuation

S. Cosgrove D. Patel.

Continued from 99

Ethanol Product slurried in ~~acetonitrile and in~~ sc H_2O

XRPD

XRPD shows no change in peak positions or relative intensities after slurrying in H_2O.

DSC: The overall appearance of the DSC does not appear to have changed: two endotherms present. There is a shift however in the low temperature peaks:

Before		After
133.9°C	⟶	130.5°C
138.2°C	⟶	137.1°C
152.7°C	⟶	152.8°C

SEM - Before: unusually smooth surfaces on some particles, some particles show mesh-like morphology.
After: Very small 'twiglet' like particles making up larger particles

Ethanol Product slurried in acetonitrile

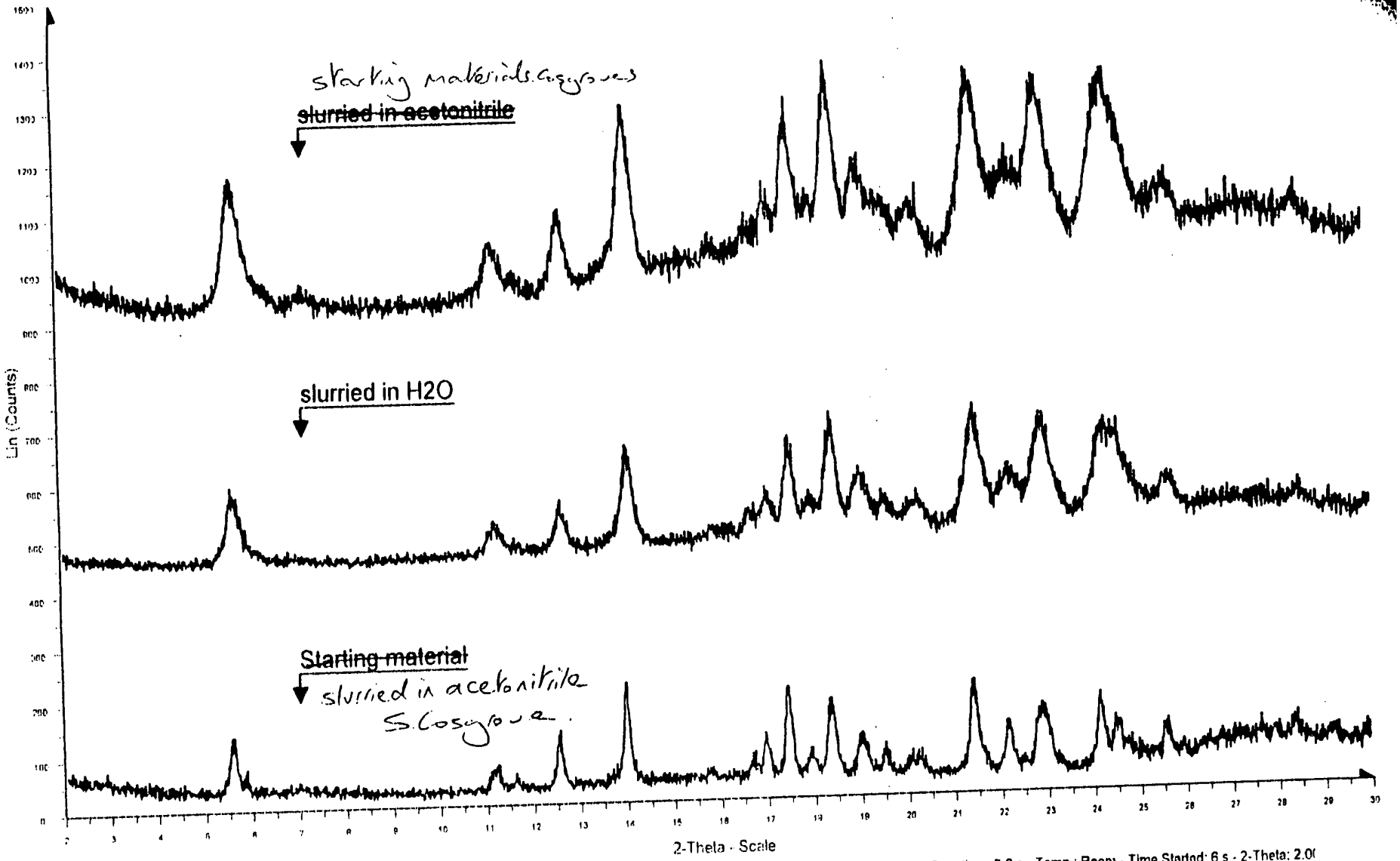
XRPD: There is no change in the XRPD pattern on slurrying in acetonitrile. This XRPD pattern is defined as ~~heat~~ sc Form III. (S32_89_aceto.ra

DSC: The three endotherms originally present merge into one:

133.9°C	⟶	133.5°C
138.2°C	⟶	X
152.7°C	⟶	X

S. Cosgrove M. Pahl

ar-c126532xx ex etoh: slurrying



ar-c126532xx ex etoh slu acetonitrile 16 d - File: 532_89_aceto.RAW - Type: 2Th/Th locked - Start: 2.000 ° - End: 30.000 ° - Step: 0.010 ° - Step time: 2.0 s - Temp.: Room - Time Started: 6 s - 2-Theta: 2.0(

Operations: Import

Y + 40.0 mm - AR-C126532xx EtOH slurried in H2O 16 d - File: 532_89_H2O.RAW - Type: 2Th/Th locked - Start: 2.000 ° - End: 30.000 ° - Step: 0.010 ° - Step time: 2.0 s - Temp.: Room - Time Started: 5 s

Operations: Import

Y + 80.0 mm - ar-c126532XX ex EtOH prior to long slurry - File: 532_149_89.RAW - Type: 2Th/Th locked - Start: 2.000 ° - End: 30.000 ° - Step: 0.010 ° - Step time: 6.0 s - Temp.: Room - Time Started: 5 s

Operations: Import

S. Cosgrove

B. Patil

532 recrystallisation using acetonitrile

10mg of micronised batch 6 AR-C126532xx was placed in a vial and 0·12mL of high purity acetonitrile added. Dissolution occurred on warming. The solution was allowed to cool slowly by placing into a water jacket filled with hot water from the tap. Excess solvent was removed by flowing N_2
Good crystals were obtained which gave a sharp diffractogram. The diffractogram did not resemble those performed previously, but requires repeating. file: 532acetonitrile.raw

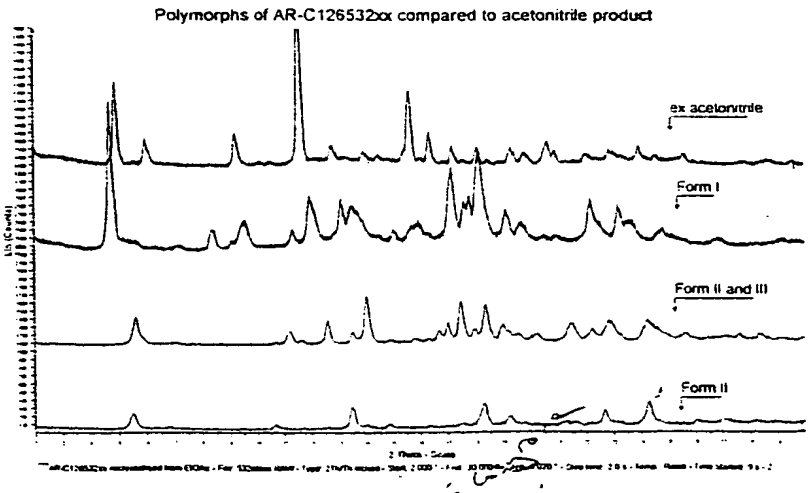
DSC, though rather noisy, evidences a single endotherm (onset 139·2°C, peak 142·2°C and ΔH 6·8 J/g). This indicates the presence of Form II.

SEM: Very large needles up to ~0·5mm.

XRPD again: XRPD of the crushed sample using a mortar + pestle is identical to that measured previously (above).
Files: 532acetonitrile.dfrw
532acetonitrile_grnd.raw

The pattern does not correspond to either Form II, III, I

XRPD and DSC defined as Polymorph IV



S. Cosgrove N. Patel 43

Multiple Cycle DSC

Aim : to distinguish between different polymorphs and to detect any interconversions.

Method : heat up to and beyond the first melting event, allow to cool naturally, then heat up to the next melting event. Therefore for 2 melting events at eg 135 and 150°C, heat to 140°C and cool then up to 155°C and cool, then up to 200°C.

Samples : AR-C126532 batch 7 – DSC shows melts at 138 (sc) 8 and 151°C
AR-C126532 batch 7 recryst from EtOAc – Dsc shows one melt at 138°C
AR-C126532 batch 7 recryst from EtOH – DSC shows melts at 131 and 138°C

Definitions : Form III melts at 131°C, Form II at 138°C and Form I at 151°C

AR-C126532 batch 7

sample 1 : ramp from 25C to 200°C
2 : ramp from 25C to 143°C, cool, ramp from 25°C to 158°C, cool, ramp to 200°C

After cooling from 143°C, an amorphous material is formed. The DSC of this material shows

	onset	Peak	ΔH
endotherm	53.7°C ✓	56.3°C ✓	1.495 J/g ✓
broad exotherm	112.8°C ✓	128.8°C ✓	−39.7 J/g ✓
endotherm	150 151.0°C ✓	153.2°C ✓	52.6 J/g ✓

The melting event at 151°C is increased in size if in comparison to that of the single ramp of sample 1 (7.3 J/g)

S. Cosgrove G Sitali PS149/24

EXHIBIT I TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
11/240,801	10/03/2005	Martin Bohlin	3764-171	2381

23117 7590 02/14/2006

NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
BERCH, MARK L	
ART UNIT	**PAPER NUMBER**
1624	

DATE MAILED: 02/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	11/240,801	BOHLIN ET AL.	
	Examiner	Art Unit	
	Mark L. Berch	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-84* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *56,57,59-66,69-75,77 and 78* is/are allowed.

6)☒ Claim(s) *67,68,76 and 79-84* is/are rejected.

7)☒ Claim(s) *58* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/3/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 67-68, 79 are rejected under 35 U.S.C. 102(e) as being anticipated by Harndern 6525060.

See example 3, which prepares the indicated compound. The reference is silent as to the physical form, or whether it is a hydrate.

MPEP 2112 states:

"SOMETHING WHICH IS OLD DOES NOT BECOME PATENTABLE UPON THE DISCOVERY OF A NEW PROPERTY 3

The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)."

In this case, the "unknown property" is the particular crystalline form(s), and the degree of hydration, if any. This is unknown because the reference is silent on this property. MPEP 2112 goes on to state:

"A REJECTION UNDER 35 U.S.C. 102/103 CAN BE MADE WHEN THE PRIOR ART PRODUCT SEEMS TO BE IDENTICAL EXCEPT THAT THE PRIOR ART IS SILENT AS TO AN INHERENT CHARACTERISTIC

Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 U.S.C. 102 and 103, expressed as a 102/103 rejection."

Again, the "CHARACTERISTIC" which the prior art is silent on is the crystalline form and degree of hydration.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is. The only difference is a characteristic about which the reference happens to be silent. See also Ex parte Anderson, 21 USPQ 2nd 1241 at 1251, discussion of Rejection E.

In order to overcome the rejection, applicants need only to replicate the prior art material and determine its properties. Claim 79 is included because the amorphous form will prepared the exact same aqueous solution as the crystalline forms.

The declaration is noted. It antedates the reference with regard to the four crystalline forms. Applicants comments are solicited on the subject of declaring an interference, in the event this case becomes allowed.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> **The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 68 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claim is drawn to an amorphous hydrate. There is no description of such a thing in the specification, and hence there is no description of how to make it either. Note that page 4 describes the amorphous material as not being a hydrate.

Claim 76 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claim says "a solvent" which means any solvent. But the specification does not actually teach that any solvent can make Form II. For example, it does not teach that one of these forms can be made from an amide, from DMSO, from a haloalkane, from a sulfone, etc. In fact, the specification says that certain things e.g. IPA/water do not make form II (page 8, lines 26-29).

Claims 80-84 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This claim language is so broad that it cannot possibly be enabled. The specification sets forth examples of this as follows: "Arterial thrombotic complications may include unstable angina, primary arterial thrombotic complications

of atherosclerosis such as thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease, myocardial infarction with or without thrombolysis, arterial complications due to interventions in atherosclerotic disease such as angioplasty, including coronary angioplasty (PTCA), endarterectomy, stent placement, coronary and other vascular graft surgery, thrombotic complications of surgical or mechanical damage such as tissue salvage following accidental or surgical trauma, reconstructive surgery including ski and muscle flaps, conditions with a diffuse thrombotic/platelet consumption component such as disseminated intravascular coagulation, thrombotic thrombocytopaenic purpura, haemolytic uraemic syndrome, thrombotic complications of septicaemia, adult respiratory distress syndrome, anti-phospholipid syndrome, heparin-induced thrombocytopaenia and pre-eclampsia/eclampsia, or venous thrombosis such as deep vein thrombosis, venoocclusive disease, haematological conditions such as myeloproliferative disease, including thrombocythaemia, sickle cell disease; or in the prevention of mechanically-induced platelet activation in vivo, such as cardiopulmonary bypass and extracorporeal membrane oxygenation (prevention of microthromboembolism), mechanically-induced platelet activation in vitro, such as use in the preservation of blood products, e.g. platelet concentrates, or shunt occlusion such as in renal dialysis and plasmapheresis, thrombosis secondary to vascular damage/inflammation such as vasculitis, arteritis, glomerulonephritis, inflammatory bowel disease and organ graft rejection, conditions such as migraine, Raynaud's phenomenon, conditions in which platelets can contribute to the underlying inflammatory disease process in the vascular wall such as atheromatous plaque formation/progression, stenosis/restenosis and in other inflammatory conditions such as asthma, in which platelets and platelet-derived factors are implicated in the immunological disease process." The examiner notes however, that asthma is not normally considered an arterial thrombotic problem. Further, this list just covers disorders where there is too much coagulation. There are still other disorders where a thrombus would be needed but does

not form (e.g. hemophilia), which would also fall within these claims, since the claim language is broad enough to cover both categories.

Further, these claims cover prevention. Even disorders which can be treated often cannot be prevented. For example, there is no such thing as pharmaceutical prevention of Peripheral vascular disease, myeloproliferative disease, adult respiratory distress syndrome, to name just three. Such a scope thus cannot possibly be deemed enabled.

Claim Objections

Claim 58 is improperly dependent on claim 56. Claim 56 covers only crystalline forms to begin with, and hence claim 58 fails to further limit.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. If you are unable to reach Dr. Shah within a 24

hour period, please contact James O. Wilson, Acting-SPE of 1624 at 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0198.

Mark Berch

Mark L. Berch
Primary Examiner
Art Unit 1624

2/3/06

EXHIBIT J TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

Atty Dkt. LCM-3764-171

C# M#

BOHLIN ET AL TC/A.U. 1624

Serial No. 11/240,801 Examiner: Berch, M.L.

Filed: October 3, 2005 Date: March 14, 2007

Title: NEW CRYSTALLINE AND AMORPHOUS FORM OF A TRIAZOLO(4,5-D)PYRIMIDINE COMPOUND

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

RESPONSE/AMENDMENT/LETTER

This is a response/amendment/letter in the above-identified application and includes an attachment which is hereby incorporated by reference and the signature below serves as the signature to the attachment in the absence of any other signature thereon.

☐ **Correspondence Address Indication Form Attached.**

Fees are attached as calculated below:

Total effective claims after amendment **31** previously paid for **29** (at least 20) = 2 x $50.00	minus highest number	$100.00 (1202)/$50.00 (2202)	$ 100.00
Independent claims after amendment **2** previously paid for **3** (at least 3) = 0 x $200.00	minus highest number	$0.00 (1201)/$0.00 (2201)	$ 0.00
If proper multiple dependent claims now added for first time, (ignore improper); add		$360.00 (1203)/$180.00 (2203)	$ 0.00
Petition is hereby made to extend the current due date so as to cover the filing date of this paper and attachment(s)	One Month Extension $120.00 (1251)/$60.00 (2251) Two Month Extensions $450.00 (1252)/$225.00 (2252) Three Month Extensions $1020.00 (1253/$510.00 (2253) Four Month Extensions $1590.00 (1254/$795.00 (2254) Five Month Extensions $2160.00 (1255/$1080.00 (2255)		$ 2160.00
Terminal disclaimer enclosed, add		$130.00 (1814)/ $65.00 (2814)	$ 0.00
☐ Applicant claims "small entity" status. ☐ Statement filed herewith			
Rule 56 Information Disclosure Statement Filing Fee		$180.00 (1806)	$ 0.00
Assignment Recording Fee		$40.00 (8021)	$ 0.00
Other:			$ **0.00**
		TOTAL FEE ENCLOSED	$ **2260.00**

The Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, in the fee(s) filed, or asserted to be filed, or which should have been filed herewith (or with any paper hereafter filed in this application by this firm) to our Account No. 14-1140. A duplicate copy of this sheet is attached.

901 North Glebe Road, 11th Floor
Arlington, Virginia 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100
LCM:lff

NIXON & VANDERHYE P.C.
By Atty: Leonard C. Mitchard, Reg. No. 29,009

Signature: _____

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

BOHLIN ET AL — Atty. Ref.: 3764-171; Confirmation No. 2381

Appl. No. 11/240,801 — TC/A.U. 1624

Filed: October 3, 2005 — Examiner: Berch, M.L.

For: NEW CRYSTALLINE AND AMORPHOUS FORM OF A TRIAZOLO(4,5-D)PYRIMIDINE COMPOUND

* * * * * * * * * * * *

March 14, 2007

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

AMENDMENT

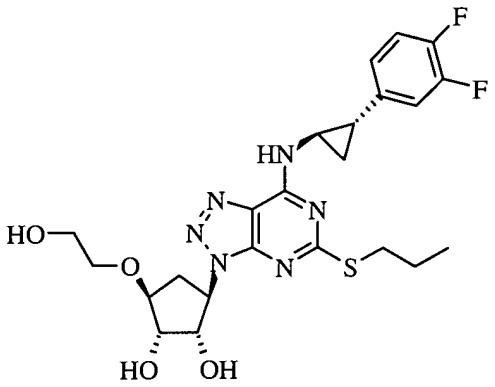
In response to the Official Action mailed February 14, 2006, please amend the above-identified application as follows:

AMENDMENTS TO THE CLAIMS:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1-55 (cancelled).

56 (previously presented). A compound of formula (I):



(I)

selected from:

a compound of formula (I) characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 5.3° (±0.1°), 20.1° (±0.1°), 20.7° (±0.1°), 21.0° (±0.1°) and 21.3° (±0.1°) 2θ;

a compound of formula (I) characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 5.5° (±0.1°), 13.5° (±0.1°), 18.3° (±0.1°), 22.7° (±0.1°) and 24.3°(±0.1°) 2θ;

a compound of formula (I) characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 14.0° (±0.1°), 17.4° (±0.1°), 18.4° (±0.1°), 21.4° (±0.1°) and 24.1°(±0.1°) 2θ; and

a compound of formula (I) characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 4.9° (±0.1°), 9.2° (±0.1°), 11.6° (±0.1°), 15.6° (±0.1°) and 16.4° (±0.1°) 2θ.

57 (previously presented). A compound of formula (I) as claimed in claim 56 that exists in an anhydrous form.

58 (canceled).

59 (previously presented). A compound of formula (I) as claimed in claim 56 characterised by an X-ray powder diffraction pattern containing specific peaks at 5.3° (±0.1°), 8.0° (±0.1º), 9.6° (±0.1°), 13.9° (±0.1°), 15.3° (±0.1°), 20.1° (±0.1°), 20.7° (±0.1°), 21.0° (±0.1º), 21.3° (±0.1°), 26.2° (±0.1°) and 27.5° (±0.1°) 2θ.

60 (previously presented). A compound of formula (I) as claimed in claim 56 characterised by a differential scanning calorimetry curve to have an onset of melting which is in the range 146 - 152°C.

61 (previously presented). A compound of formula (I) as claimed in claim 56 characterised by an X-ray powder diffraction pattern containing specific peaks at 5.5° (±0.1°), 6.8° (±0.1°), 10.6° (±0.1°), 13.5° (±0.1°), 14.9° (±0.1°), 18.3° (±0.1°), 19.2° (±0.1 °), 22.7° (±0.1°), 24.3° (±0.1°) and 27.1° (±0.1°) 2θ.

62 (previously presented). A compound of formula (I) as claimed in claim 56 characterised by a differential scanning calorimetry curve to have an onset of melting which is in the range 136-139°C.

63 (previously presented). A compound of formula (I) as claimed in claim 56 characterised by an X-ray powder diffraction pattern containing specific peaks at 5.6° (±0.1°), 12.5° (±0.1°), 14.0° (±0.1°), 17.4° (±0.1°), 18.4° (±0.1°), 21.4° (±0.1°), 22.2° (±0.1°), 22.9° (±0.1°), 24.1° (±0.1°) and 24.5° (±0.1°) 2θ.

64 (previously presented). A compound of formula (I) as claimed in claim 56 characterised by a differential scanning calorimetry curve to have an onset of melting which is in the range 127-132°C.

65 (previously presented). A compound of formula (I) as claimed in claim 56 characterised by an X-ray powder diffraction pattern containing specific peaks at 4.9° (±0.1°), 6.0° (±0.1°), 9.2° (±0.1°), 11.6° (±0.1°), 12.8° (±0.1°), 15.6° (±0.1°), 16.4° (±0.1°), 17.2° (±0.1°) and 18.1° (±0.1°) 2θ.

66 (previously presented). A compound of formula (I) as claimed in claim 56 characterised by a differential scanning calorimetry curve to have an onset of melting which at approximately 139°C.

67-68 (canceled).

69 (previously presented). A process for the preparation of a compound as claimed in claim 56, comprising crystallizing a compound of formula (I) from a solvent selected from the group consisting of a lower alkyl acetate, a lower alkyl alcohol, an aliphatic hydrocarbon, an aromatic hydrocarbon, a dialkyl ether, a dialkyl ketone, acetonitrile, water, and a mixture thereof.

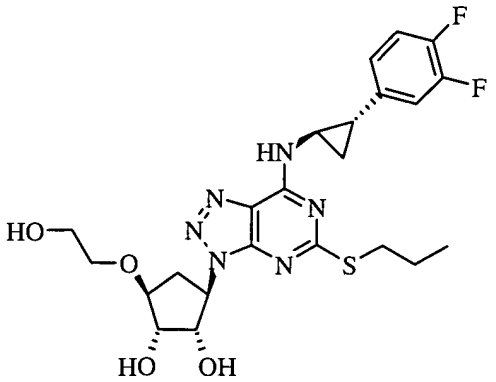
70 (previously presented). A process as claimed in claim 69, wherein the solvent is selected from the group consisting of ethanol, ethyl acetate, *iso*-propanol, *iso*-octane, acetonitrile, water, and a mixture thereof.

71 (previously presented). A process as claimed in claim 70 wherein the solvent is selected from the group consisting of a mixture of methanol and water, ethanol, ethyl acetate, a mixture of ethanol and water, a mixture of *iso*-propanol and water, a mixture of ethyl acetate and *iso*-octane, and acetonitrile.

72 (previously presented). A process for the production of a compound of formula (I) as claimed in claim 56, characterised by an X-ray powder diffraction pattern containing specific peaks at 5.3° (±0.1°), 20.1° (±0.1°), 20.7° (±0.1°), 21.0° (±0.1°) and 21.3° (±0.1°) 2θ, comprising crystallizing the compound of formula (I) from a mixture of methanol and water.

73 (previously presented). A process as claimed in claim 72 which includes the step of using a seed.

74 (previously presented). A process according to claim 73 in which the seed is prepared by melting a compound of formula (I):



(I)

characterized by an X-ray powder diffraction pattern containing specific peaks of high intensity at 5.3° (±0.1°), 8.0° (±0.1º), 9.6° (±0.1°), 13.9° (±0.1°), 15.3° (±0.1°), 20.1° (±0.1°), 20.7° (±0.1°), 21.0° (±0.1º), 21.3° (±0.1°), 26.2° (±0.1°) and 27.5° (±0.1°) 2θ.

75 (previously presented). A process for the production of a compound of formula (I) as claimed in claim 56, characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 14.0° (±0.1°), 17.4°(±0.1°), 18.4° (±0.1°), 21.4° (±0.1°) and 24.1°(±0.1°) 2θ, comprising crystallizing the compound of formula (I) from an alcohol.

76 (currently amended). A process for the production of a compound of formula (I) as claimed in claim 56, characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 5.5° (±0.1°), 13.5°(±0.1°), 18.3° (±0.1°), 22.7° (±0.1°) and 24.3°(±0.1°) 2θ, comprising crystallizing the compound of formula (I) from a solvent selected from the group consisting of ethyl acetate and chloroform.

77 (previously presented). A process for the production of a compound of formula (I) as claimed in claim 56, characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 14.0° (±0.1°), 17.4°(±0.1°), 18.4° (±0.1°), 21.4° (±0.1°) and 24.1°(±0.1°) 2θ, comprising slurrying a compound of formula (I) in an IPA/water solvent system at a temperature of 5 to 65°C.

78 (previously presented). A process for the production of a compound of formula (I) as claimed in claim 56, characterised by an X-ray powder diffraction pattern containing specific peaks of high intensity at 4.9° (±0.1°), 9.2° (±0.1°), 11.6° (±0.1°), 15.6° (±0.1°) and 16.4° (±0.1°) 2θ, comprising crystallizing the compound of formula (I) from acetonitrile.

79 (previously presented). A pharmaceutical composition comprising a compound as claimed in claim 56 in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

80 (currently amended). A method of treatment ~~or prevention~~ of arterial thrombotic complications selected from the group consisting of unstable angina, thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease and myocardial infarction in patients with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from ~~or susceptible to~~ such a disorder a therapeutically effective amount of a compound as claimed in claim 56.

81 (currently amended). A method of treatment ~~or prevention~~ of arterial thrombotic complications selected from the group consisting of unstable angina, thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease and myocardial infarction in patients with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from ~~or~~

~~susceptible to~~ such a disorder a therapeutically effective amount of a compound as claimed in claim 59.

82 (currently amended). A method of treatment ~~or prevention~~ of arterial thrombotic complications selected from the group consisting of unstable angina, thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease and myocardial infarction in patients with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from ~~or susceptible to~~ such a disorder a therapeutically effective amount of a compound as claimed in claim 61.

83 (currently amended). A method of treatment ~~or prevention~~ of arterial thrombotic complications selected from the group consisting of unstable angina, thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease and myocardial infarction in patients with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from ~~or susceptible to~~ such a disorder a therapeutically effective amount of a compound as claimed in claim 63.

84 (currently amended). A method of treatment ~~or prevention~~ of arterial thrombotic complications selected from the group consisting of unstable angina, thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease and myocardial infarction in patients with coronary artery, cerebrovascular or peripheral

vascular disease, which comprises administering to a person suffering from ~~or susceptible to~~ such a disorder a therapeutically effective amount of a compound as claimed in claim 65.

85 (new). A method of treatment of an arterial thrombotic complication in a patient with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from such a disorder a therapeutically effective amount of a compound as claimed in claim 56, wherein the arterial thrombotic complication is an arterial complication due to angioplasty, endarterectomy, stent placement, vascular graft surgery and thrombotic complications of surgical or mechanical damage.

86 (new). A method of treatment of an arterial thrombotic complication in a patient with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from such a disorder a therapeutically effective amount of a compound as claimed in claim 59, wherein the arterial thrombotic complication is an arterial complication due to angioplasty, endarterectomy, stent placement, vascular graft surgery and thrombotic complications of surgical or mechanical damage.

87 (new). A method of treatment of an arterial thrombotic complication in a patient with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from such a disorder a therapeutically

effective amount of a compound as claimed in claim 61, wherein the arterial thrombotic complication is an arterial complication due to angioplasty, endarterectomy, stent placement, vascular graft surgery and thrombotic complications of surgical or mechanical damage.

88 (new). A method of treatment of an arterial thrombotic complication in a patient with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from such a disorder a therapeutically effective amount of a compound as claimed in claim 63, wherein the arterial thrombotic complication is an arterial complication due to angioplasty, endarterectomy, stent placement, vascular graft surgery and thrombotic complications of surgical or mechanical damage.

89 (new). A method of treatment of an arterial thrombotic complication in a patient with coronary artery, cerebrovascular or peripheral vascular disease, which comprises administering to a person suffering from such a disorder a therapeutically effective amount of a compound as claimed in claim 65, wherein the arterial thrombotic complication is an arterial complication due to angioplasty, endarterectomy, stent placement, vascular graft surgery and thrombotic complications of surgical or mechanical damage.

REMARKS/ARGUMENTS

Reconsideration of this application is requested. Claims 56, 57 and 59-66, 69-89 are in the case.

I. THE INTERVIEW

This will acknowledge the interview conducted with the Examiner (Dr. Berch) on March 14, 2007. During the interview, the Examiner indicated that the outstanding Action should have been **non-final**, and the final action language appearing on page 6 of the Action was included inadvertently. It was agreed, therefore, that the present Amendment and extension request will be considered timely, and that an RCE is **not** required to secure entry of the Amendment.

II. ALLOWED CLAIMS

It is noted, with appreciation, that claims 56, 57, 59-66, 69-75, 77 and 78 are allowed.

III. THE ANTICIPATION REJECTION

Claims 67, 68 and 79 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by U.S. Patent 6,525,060. That rejection is respectfully traversed.

With out conceding to the merit of the rejection, claims 67 and 68 have been canceled without prejudice. With regard to claim 79, this claim is dependent on allowed claim 56 and, therefore, should also be allowed. Withdrawal of the rejection of claim 79 is respectfully requested.

On page 3 of the Action, the Examiner has requested Applicants' comments with respect to the subject of declaring an interference. The Examiner is advised that the cited Hardern U.S. Patent 6,525,060 and the present application are commonly owned by AstraZeneca AB. As the two cases are commonly assigned, no interference should be declared.

IV. THE 35 U.S.C. §112, FIRST PARAGRAPH, REJECTIONS

Claims 68, 76 and 80-84 stand rejected under 35 U.S.C. §112, first paragraph, for the reasons detailed on pages 4-6 of the Action. Those rejections are respectfully traversed.

Claim 68 has been canceled without prejudice. The rejection of that claim has accordingly been rendered moot.

With reference to claim 76, the solvent has been further defined to be selected from ethyl acetate and chloroform. Support for this amendment appears in the description at page 8 and in Example 2. Withdrawal of this rejection is respectfully requested.

With regard to claims 80-84, while Applicants do not agree with the Examiner's position, in order to expedite prosecution, claims 80-84 have been amended to delete the term "prevention" without prejudice, and to further amend the claims to define arterial thrombotic complications as being selected from unstable angina, thrombotic or embolic stroke, transient ischaemic attacks, peripheral vascular disease and myocardial infraction. Additional independent claims 85-89 have also been presented where the artial thrombotic complication is defined as an arterial complication due to angioplasty,

endarterectomy, stint replacement, vascular graft surgery and thrombotic complications of surgical or mechanical damage. These claims are supported and enabled by a specification at, for example, pages 9-10, which describes the compounds as P_{2T} receptor antagonists.

Withdrawal of the outstanding 35 U.S.C. §112, first paragraph, rejection is now believed to be in order. Such action is respectfully requested.

V. CLAIM OBJECTION

Claim 58 has been objected to as not properly dependent on claim 56. In response, and without conceding to the merit of this rejection, claim 58 has been cancelled without prejudice. Withdrawal of the claim rejection is now respectfully requested.

Favorable action is awaited.

Respectfully submitted,

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EXHIBIT K TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

Chapter 2300 Interference Proceedings

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2301 Introduction [R-4]

An interference is a contest under 35 U.S.C. 135(a) between an application and either another application or a patent. An interference is declared to assist the Director of the United States Patent and Trademark Office in determining priority, that is, which party first invented the commonly claimed invention within the meaning of 35 U.S.C. 102(g)(1). See MPEP § 2301.03. Once an interference has been suggested under 37 CFR 41.202, the examiner refers the suggested interference to the Board of Patent Appeals and Interferences (Board). An administrative patent judge declares the interference, which is then administered at the Board. A panel of Board members enters final judgment on questions of priority and patentability arising in an interference.

Once the interference is declared, the examiner generally will not see the application again until the interference has been terminated. Occasionally, however, the Board may refer a matter to the examiner or may consult with the examiner on an issue. Given the very tight deadlines in an interference, any action on a consultation or referral from the Board must occur with special dispatch.

The application returns to the examiner after the interference has been terminated. Depending on the nature of the judgment in the case, the examiner may need to take further action in the application. For instance, if there are remaining allowable claims, the application may need to be passed to issue. The Board may have entered a recommendation for further action by the examiner in the case. If the applicant has lost an issue in the interference, the applicant may be barred from taking action in the application or any subsequent application that would be inconsistent with that loss.

Given the infrequency, cost, and complexity of interferences, it is important for the examiner to consult immediately with an Interference Practice Specialist (IPS) in the examiner's Technology Center, see MPEP § 2302, once a possible interference is identified. It is also important to complete examination before the possible interference is referred to the Board. See MPEP § 2303.<

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2301.01 Statutory Basis [R-4]

35 U.S.C. 102. Conditions for patentability; novelty and loss of right to patent.

A person shall be entitled to a patent unless —

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(g)(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not abandoned, suppressed, or concealed, or

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35 U.S.C. 104. Invention made abroad.

(a) IN GENERAL.—

(1) PROCEEDINGS.—In proceedings in the Patent and Trademark Office, in the courts, and before any other competent authority, an applicant for a patent, or a patentee, may not establish a date of invention by reference to knowledge or use thereof, or other activity with respect thereto, in a foreign country other than a NAFTA country or a WTO member country, except as provided in sections 119 and 365 of this title.

(2) RIGHTS.—If an invention was made by a person, civil or military—

(A) while domiciled in the United States, and serving in any other country in connection with operations by or on behalf of the United States,

(B) while domiciled in a NAFTA country and serving in another country in connection with operations by or on behalf of that NAFTA country, or

(C) while domiciled in a WTO member country and serving in another country in connection with operations by or on behalf of that WTO member country, that person shall be entitled to the same rights of priority in the United States with respect to such invention as if such invention had been made in the United States, that NAFTA country, or that WTO member country, as the case may be.

(3) USE OF INFORMATION.—To the extent that any information in a NAFTA country or a WTO member country concerning knowledge, use, or other activity relevant to proving or disproving a date of invention has not been made available for use in a proceeding in the Patent and Trademark Office, a court, or any other competent authority to the same extent as such information could be made available in the United States, the Director, court, or such other authority shall draw appropriate inferences, or take other action permitted by statute, rule, or regulation, in favor of the party that requested the information in the proceeding.

(b) DEFINITIONS.—As used in this section—

(1) The term "NAFTA country" has the meaning given that term in section 2(4) of the North American Free Trade Agreement Implementation Act; and

(2) The term "WTO member country" has the meaning given that term in section 2(10) of the Uruguay Round Agreements Act.

35 U.S.C. 135. Interferences.

(a) Whenever an application is made for a patent which, in the opinion of the Director, would interfere with any pending application, or with any unexpired patent, an interference may be declared and the Director shall give notice of such declaration to the applicants, or applicant and patentee, as the case may be. The Board of Patent Appeals and Interferences shall determine questions of priority of the inventions and may determine questions of patentability. Any final decision, if adverse to the claim of an applicant, shall constitute the final refusal by the Patent and Trademark Office of the claims involved, and the Director may issue a patent to the applicant who is adjudged the prior inventor. A final judgment adverse to a patentee from which no appeal or other review has been or can be taken or had shall constitute cancellation of the claims involved in the patent, and notice of such cancellation shall be endorsed on copies of the patent distributed after such cancellation by the Patent and Trademark Office.

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2301.02 Definitions [R-4]

37 CFR 41.2. Definitions.

Unless otherwise clear from the context, the following definitions apply to proceedings under this part:

Affidavit means affidavit, declaration under § 1.68 of this title, or statutory declaration under 28 U.S.C. 1746. A transcript of an ex parte deposition may be used as an affidavit in a contested case.

Board means the Board of Patent Appeals and Interferences and includes:

(1) For a final Board action:

(i) In an appeal or contested case, a panel of the Board.

(ii) In a proceeding under § 41.3, the Chief Administrative Patent Judge or another official acting under an express delegation from the Chief Administrative Patent Judge.

(2) For non-final actions, a Board member or employee acting with the authority of the Board.

Board member means the Under Secretary of Commerce for Intellectual Property and Director of the United States Patent and Trademark Office, the Deputy Under Secretary of Commerce for Intellectual Property and Deputy Director of the United States Patent and Trademark Office, the Commissioner for Patents, the Commissioner for Trademarks, and the administrative patent judges.

Contested case means a Board proceeding other than an appeal under 35 U.S.C. 134 or a petition under § 41.3. An appeal in an inter partes reexamination is not a contested case.

Final means, with regard to a Board action, final for the purposes of judicial review. A decision is final only if:

(1) *In a panel proceeding.* The decision is rendered by a panel, disposes of all issues with regard to the party seeking judicial review, and does not indicate that further action is required; and

(2) *In other proceedings*. The decision disposes of all issues or the decision states it is final.

Hearing means consideration of the issues of record. *Rehearing* means reconsideration.

Office means United States Patent and Trademark Office.

Panel means at least three Board members acting in a panel proceeding.

Panel proceeding means a proceeding in which final action is reserved by statute to at least three Board members, but includes a

non-final portion of such a proceeding whether administered by a panel or not.

Party, in this part, means any entity participating in a Board proceeding, other than officers and employees of the Office, including:

(1) An appellant;

(2) A participant in a contested case;

(3) A petitioner; and

(4) Counsel for any of the above, where context permits.

37 CFR 41.100. Definitions.

In addition to the definitions in § 41.2, the following definitions apply to proceedings under this subpart:

Business day means a day other than a Saturday, Sunday, or Federal holiday within the District of Columbia.

Involved means the Board has declared the patent application, patent, or claim so described to be a subject of the contested case.

37 CFR 41.200. Procedure; pendency.

(a) A patent interference is a contested case subject to the procedures set forth in subpart D of this part.

(b) A claim shall be given its broadest reasonable construction in light of the specification of the application or patent in which it appears.

(c) Patent interferences shall be administered such that pendency before the Board is normally no more than two years.

37 CFR 41.201. Definitions.

In addition to the definitions in §§ 41.2 and 41.100, the following definitions apply to proceedings under this subpart:

Accord benefit means Board recognition that a patent application provides a proper constructive reduction to practice under 35 U.S.C. 102(g)(1).

Constructive reduction to practice means a described and enabled anticipation under 35 U.S.C. 102(g)(1) in a patent application of the subject matter of a count. *Earliest constructive reduction to practice* means the first constructive reduction to practice that has been continuously disclosed through a chain of patent applications including in the involved application or patent. For the chain to be continuous, each subsequent application must have been co-pending under 35 U.S.C. 120 or 121 or timely filed under 35 U.S.C. 119 or 365(a).

Count means the Board's description of the interfering subject matter that sets the scope of admissible proofs on priority. Where there is more than one count, each count must describe a patentably distinct invention.

Involved claim means, for the purposes of 35 U.S.C.135(a), a claim that has been designated as corresponding to the count.

Senior party means the party entitled to the presumption under § 41.207(a)(1) that it is the prior inventor. Any other party is a *junior party*.

Threshold issue means an issue that, if resolved in favor of the movant, would deprive the opponent of standing in the interference. Threshold issues may include:

(1) No interference-in-fact, and

(2) In the case of an involved application claim first made after the publication of the movant's application or issuance of the movant's patent:

(i) Repose under 35 U.S.C. 135(b) in view of the movant's patent or published application, or

(ii) Unpatentability for lack of written description under 35 U. S.C. 112(1) of an involved application claim where the applicant suggested, or could have suggested, an interference under § 41.202(a).<

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2301.03 Interfering Subject Matter [R-4]

37 CFR 41.203. Declaration.

(a) *Interfering subject matter*. An interference exists if the subject matter of a claim of one party would, if prior art, have anticipated or rendered obvious the subject matter of a claim of the opposing party and vice versa.

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A claim of one inventor can be said to interfere with the claim of another inventor if they each have a patentable claim to the same invention. The Office practice and the case law define "same invention" to mean patentably indistinct inventions. *Case v. CPC Int'l, Inc.*, 730 F.2d 745, 750, 221 USPQ 196, 200 (Fed. Cir. 1984); *Aelony v. Arni*, 547 F.2d 566, 570, 192 USPQ 486, 489-90 (CCPA 1977); *Nitz v. Ehrenreich*, 537 F.2d 539, 543, 190 USPQ 413, 416 (CCPA 1976); *Ex parte Card*, 1904 C.D. 383, 384-85 (Comm'r Pats. 1904). If the claimed invention of either party is patentably distinct from the claimed invention of the other party, then there is no interference-in-fact. *Nitz v. Ehrenreich*, 537 F.2d 539, 543, 190 USPQ 413, 416 (CCPA 1976). 37 CFR 41.203(a) states the test in terms of the familiar concepts of obviousness and anticipation. Accord *Eli Lilly & Co. v. Bd. of Regents of the Univ. of Wa.*, 334 F.3d 1264, 1269-70, 67 USPQ2d 1161, 1164-65 (Fed. Cir. 2003) (affirming the Office's interpretive rule).

Identical language in claims does not guarantee that they are drawn to the same invention. Every claim must be construed in light of the application in which it appears. 37 CFR 41.200(b). Claims reciting means-plus-function limitations, in particular, might have different scopes depending on the corresponding structure described in the written description.

When an interference is declared, there is a description of the interfering subject matter, which is called a "count." Claim correspondence identifies claims that would no longer be allowable or patentable to a party if it loses the priority determination for the count. To determine whether a claim corresponds to a count, the

subject matter of the count is assumed to be prior art to the party. If the count would have anticipated or supported an obviousness determination against the claim, then the claim corresponds to the count. 37 CFR 41.207(b)(2). Every count must have at least one corresponding claim for each party, but it is possible for a claim to correspond to more than one count.

Example 1

A patent has a claim to a compound in which R is an alkyl group. An application has a claim to the same compound except that R is n-pentyl, which is an alkyl. The application claim, if prior art to the patent, would have anticipated the patent claim. The patent claim would not have anticipated the application claim. If, however, in the art n-pentyl would have been an obvious choice for alkyl, then the claims define interfering subject matter.

Example 2

An application has a claim to a boiler with a novel safety valve. A patent has a claim to just the safety valve. The prior art shows that the need for boilers to have safety valves is well established. The application claim, when treated as prior art, would have anticipated the patent claim. The patent claim, when treated as prior art and in light of the boiler prior art, can be shown to render the application claim obvious. The claims interfere.

Example 3

An application has a claim to a reaction using platinum as a catalyst. A patent has a claim to the same reaction except the catalyst may be selected from the Markush group consisting of platinum, niobium, and lead. Each claim would have anticipated the other claim when the Markush alternative for the catalyst is platinum. The claims interfere.

Example 4

Same facts as Example 3, except the applicant has a Markush group for the catalyst consisting of platinum, osmium, and zinc. Each claim would have anticipated the other claim when the Markush alternative for the catalyst in each claim is platinum. The claims interfere.

Example 5

An application has a claim to a protein with a specific amino acid sequence shown in SEQ ID NO:1. A patent has a claim to the genus of polynucleotides defined as encoding the same amino acid sequence as the applicant's SEQ ID NO:1. The patent claim would have anticipated the application claim since it expressly describes an amino acid sequence identical to the protein of the application. The application claim would have rendered the patent claim obvious in light of a well-established relationship between nucleic acids for encoding amino acids in protein sequences. The claims interfere.

Example 6

A patent has a claim to a genus of polynucleotides that encode a protein with a specific amino acid sequence. An application has a claim to a polynucleotide that encodes a protein with the same amino acid sequence. The application claim is a species within the genus and thus would have anticipated the patent claim. The patent claim would not have anticipated or rendered the application claim obvious without some explanation of why a person having ordinary skill in the art would have selected the applicant's species from the patentee's genus. Generally the explanation should include citation to prior art supporting the obviousness of the species. Without the explanation, the claims do not interfere.

Example 7

A patent and an application each claim the same combination including "means for fastening." The application discloses glue for fastening, while the patent discloses a rivet for fastening. Despite otherwise identical claim language, the claims do not interfere unless it can be shown that in this art glue and rivets were considered structurally equivalent or would have rendered each other obvious.

Example 8

A patent claims a formulation with the surfactant sodium lauryl sulfate. An application claims the same formulation except no specific surfactant is described. The application discloses that it is well known in the art to use sodium lauryl sulfate as the surfactant in these types of formulations. The claims interfere.

Example 9

An applicant has a claim to a genus and a species within the genus. The interference is declared with two counts, one directed to the genus and one directed to the species. The species claim would correspond to the species count because the count would have anticipated the claimed subject matter. The genus count would not ordinarily have anticipated the species claim, however, so the species claim would only correspond to the genus count if there was a showing that the genus count would have rendered the claimed species obvious. The genus claim, however, would have been anticipated by both the genus count and the species count and thus would correspond to both counts.<

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2302 Consult an Interference Practice Specialist [R-4]

Every Technology Center (TC) has at least one Interference Practice Specialist (IPS), who must be consulted when suggesting an interference to the Board of Patent Appeals and Interferences (Board).

Less than one percent of all applications become involved in an interference. Consequently, examiners are not expected to become experts in interference practices. Instead, examiners are expected to be proficient in identifying potential interference and to consult with an IPS in their TC on interference matters. The IPS, in turn, is knowledgeable about when and how to suggest interferences, how to handle inquiries to and from the Board before and during interferences, and how to handle applications after interferences are completed.

An IPS must approve any referral of a suggested interference to the Board. The referral must include a completed Form PTO-850, which either an IPS or a Director of the examiner's TC must sign.

IPSs consult with administrative patent judges (APJs) that declare interferences to stay current in interference practice. When necessary, an IPS may arrange for a consultation with an APJ to discuss a suggested interference or the effect of a completed interference. Examiners must promptly address inquiries or requests from an IPS regarding a suggested interference.

Form PTO-850-(Rev. 09-30-2005)

DO NOT SCAN - PREDECISIONAL MEMORANDUM
SUGGESTED INTERFERENCE REFERRAL

Count #_____

To the Board of Patent Appeals and Interferences:

An interference is suggested involving the following (insert number) ____ parties—

PARTY	APPLICATION NO.* ☐	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
If the involved case is a patent, have its maintenance fees been paid? Yes ☐ No ☐			Not due yet ☐ In grace period ☐	
The claim(s) of this party corresponding to this count:			Claim(s) NOT corresponding to this count:	

Proposed priority benefit (list all intervening applications necessary for continuity)

COUNTRY Translation?	APPLICATION NO.*	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
☐	☐			
☐	☐			
☐	☐			
☐	☐			
☐	☐			

PARTY	APPLICATION NO.* ☐	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
If the involved case is a patent, have its maintenance fees been paid? Yes ☐ No ☐			Not due yet ☐ In grace period ☐	
The claim(s) of this party corresponding to this count:			Claim(s) NOT corresponding to this count:	

Proposed priority benefit (list all intervening applications necessary for continuity)

COUNTRY Translation?	APPLICATION NO.*	FILING DATE	PATENT NO., IF ANY	ISSUE DATE, IF ANY
☐	☐			
☐	☐			
☐	☐			
☐	☐			
☐	☐			

INSTRUCTIONS *(Check off each step, if applicable)*

- ☐ 1. Obtain all files listed above. IFW files should be messaged to the mailbox **BPAI.Inbox**.
- ☐ 2. Confirm that the proposed involved claims are still active and all corrections and entered amendments have been considered. The patents must not be expired for, among other things, failure to pay a maintenance fee (Check RAM File History).
- ☐ 3. If one of the involved or benefit files is a published application or a patent, check for compliance with 35 U.S.C. 135(b).
- ☐ 4. Obtain a certified translation of any non-English language benefit or PCT document (37 CFR 1.55(a)) if not already in file.
- ☐ 5. Attach an explanation of why the claims interfere.
- ☐ 6. Discuss the proposed interference with an Interference Practice Specialist in your Technology Center.

DATE	PRIMARY EXAMINER (name & signature)	ART UNIT	TELEPHONE NO.
DATE	INTERFERENCE PRACTICE SPECIALIST or TC DIRECTOR (name & signature)		TELEPHONE NO.

*For each application listed, check the box if a paper file or artifact file is associated with the application.

Page_____of _____

GENERAL PRACTICES

Practice 1. Consult an Interference Practice Specialist.

In an effort to maximize uniformity, when an examiner first becomes aware that a potential interference exists or any other interference issue arises during prosecution of an application, the examiner should bring the matter to the attention of an IPS in the examiner's TC.

The IPS in turn will consult with an APJ designated from time to time by the Chief Administrative Patent Judge.

A plan of action will be developed on a case-by-case basis.

Practice 2. Party not in condition for allowance.

When:

(A) a first application and a second application claim the same patentable invention; and

(B) a first application is in condition for allowance; and

(C) the second application is not in condition for allowance,

then generally a notice of allowance should be entered in the first application and it should become a patent.

Without suspending action in the first application and after consultation consistent with Practice 1 above, the examiner may wish to give the second applicant a very brief period of time within which to put the second application in condition for allowance, e.g., by canceling rejected claims thereby leaving only allowable claims which interfere with the claims of the first application.

When examination of the second application is complete, an application versus patent interference may be appropriate.

Practice 3. Both in condition for allowance; earliest effective filing dates within six months.

When two applications are in condition for allowance and the earliest effective filing dates of the applications are within six months of each other, an application versus application interference may be suggested, provided the applicant with the later filing date makes the showing required by 37 CFR 41.202(d). Note that if the earliest filed application is available as a reference (for example, as a published application under 35 U.S.C. 102(e)) against the other application, then a rejection should be made against the other application. Ideally, the rejection would be made early in the prosecution, but if it is not and as a result the junior application is not in condition for allowance, then the senior application should be issued. In light of patent term adjustments it is no longer appropriate to suspend an application on the chance that an interference might ultimately result.

Practice 4. Both in condition for allowance; earliest effective filing dates not within six months.

If the applications are both in condition for allowance and earliest effective filing dates of the applications are not within six months of each other, the application with the earliest effective filing date shall be issued. The application with the later filing date shall be rejected on the basis of the application with the earliest effective filing date. Further action in the application with the later filing date will be governed by prosecution in that application. If the applicant in the application with the later filing date makes the showing required by 37 CFR 41.202(d), an application versus patent interference may be declared. If no rejection is possible over the patent issuing from the application with the earliest effective filing date, then the applicant must still be required under 35 U.S.C. 132 to make the priority showing required in 37 CFR 41.202(d).

Practice 5. Suspension discouraged.

Suspension of prosecution pending a possible interference should be rare and should not be entered prior to the consultation required by Practice 1 above.<

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2303 Completion of Examination [R-4]

37 CFR 41.102. Completion of examination.

Before a contested case is initiated, except as the Board may otherwise authorize, for each involved application and patent:

(a) Examination or reexamination must be completed, and

(b) There must be at least one claim that:

(1) Is patentable but for a judgment in the contested case, and

(2) Would be involved in the contested case.

An interference should rarely be suggested until examination is completed on all other issues. Each

pending claim must be allowed, finally rejected, or canceled. Any appeal from a final rejection must be completed, including any judicial review. Any petition must be decided.

Example 1

An applicant has one allowed claim directed to invention A, which is the same invention of another inventor within the meaning of 35 U.S.C. 102(g)(1), and has rejected claims directed to different invention B. If the rejection is contested, the application is not yet ready for an interference. Restriction of the application to invention A, followed by cancellation of the claims directed to invention B would remove this impediment to declaring an interference.

Example 2

A patent has a claim to a species. An applicant has claims to the species and to a genus that includes the species. The examiner has allowed the species claim, but rejected the genus claim. The applicant suggests an interference with the patent. The interference will generally not be declared until the applicant resolves the status of the genus claim by, for example, appealing the rejection or canceling the rejected claim. An applicant may expedite the process of having the interference declared by canceling the genus claim from the application.

Two grounds of unpatentability receive particularly close scrutiny before an interference is declared. Enforcement of the written description requirement under 35 U.S.C. 112, first paragraph and the late claiming bars under 35 U.S.C. 135(b) are important to preserve the efficiency and integrity of interferences. 37 CFR 41.201, "Threshold issue." See, e.g., *Berman v. Housey*, 291 F.3d 1345, 1354, 63 USPQ2d 1023, 1029 (Fed. Cir. 2002).

RESTRICTION IN APPLICATIONS WITH INTERFERING CLAIMS

Ordinarily restrictions are limited to situations where (A) the inventions are independent or distinct as claimed, and (B) there would be a serious burden on the examiner if restriction is not required (see MPEP § 803). Potential interferences present an additional situation in which a restriction requirement may be appropriate. Specifically, restriction of interfering claims from non-interfering claims, or from unpatentable claims whose further prosecution would unduly delay initiation of an interference, can be an appropriate use of restrictions under 35 U.S.C. 121. An Interference Practice Specialist (IPS) should be consulted in making and resolving restrictions under this heading. An applicant may, of course, also choose to cancel claims and refile them in a continuation application without waiting for the restriction requirement.

A. Non-Interfering Claims

Patent term adjustments are available for patents whose issuance has been delayed for an interference. 35 U.S.C. 154(b)(1)(C)(i). A claim that does not interfere, by definition, is directed to a patentably distinct invention compared to a claim that does interfere. Leaving a non-interfering claim in an application going into an interference creates an unwarranted delay in the issuance of claims to the non-interfering subject matter. As far as the public and the Office are concerned, there is no justification for not issuing the non-interfering claims promptly. An exception exists if the claims are already term limited, as would be the case for an application subject to a terminal disclaimer or a reissue application (see 35 U.S.C. 154(b)(1)(C) (referring to issuance of the original patent)).

If an application contains both interfering and non-interfering claims, a restriction requirement should be made between the two. If the applicant traverses the restriction requirement, depending on the reasons for the traversal, the restriction may be maintained or the traversal may be treated as a concession that the non-interfering claims should be designated as corresponding to the count.

B. Unpatentable Claims

Ordinarily restriction of claims simply because they are not patentable would not be appropriate. If, however, (A) prosecution of the unpatentable claims to completion would unduly delay initiation of the interference and (B) the delay would create prejudice to another stakeholder, such as another applicant or the public, a restriction requirement may be appropriate. Approval of an IPS is required before this restriction requirement may be made.

Example

An applicant has both broad and narrow claims. The narrow claims are plainly supported, but the support for the broad claims is contested. A patent with claims to the narrow invention issues to another inventor with a much later earliest effective filing date. Delay of the interference until the patentability of the broader claims is resolved may unduly prejudice the patentee and the public by leaving a cloud of doubt hanging over the patent claims.

If the unpatentable application claims are eventually prosecuted to allowance, the examiner should consult with the IPS regarding the status of the interference in case the claims would be affected by the outcome of the interference.

C. Reissue Applications

As explained above, reissue applications are not subject to patent term adjustments. Applicants sometimes, however, file reissue applications to amend patent claims in response to events occurring in the interference. To maintain parity with other applicants, the Board does not permit reissue applicants to add claims that would not correspond to a count. *Winter v. Fujita*, 53 USPQ2d 1234, 1249 (Bd. Pat. App. & Inter. 1999). Since the burden lies with the reissue applicant to comply with *Winter*, the examiner need not require restriction of the non-interfering claims. Practice under *Winter*, however, may explain why some reissue applicants file more than one reissue application for the same patent.

Form paragraph 23.01 may be used to acknowledge a request for interference that is premature since examination of the application has not been completed.

¶ *23.01 Request for Interference Premature; Examination Not Completed*

The request for interference filed **[1]** is acknowledged. However, examination of this application has not been completed as required by 37 CFR 41.102(a). Consideration of a potential interference is premature. See MPEP § 2303.

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2303.01 Issuance and Suspension [R-4]

Since applicants may be eligible for patent term adjustments to offset delays in examination, 35 U.S.C. 154(b)(1), it is important that suspensions should rarely, if ever, be used and that applications with allowed claims be issued to the greatest extent possible.

Example 1

A claim of patent A and a claim of application B interfere. Examination of application B is completed. An interference may not be declared between two patents. 35 U.S.C. 135(a). Consequently, the interfering claim in application B should not be passed to issue, even if it has an earlier effective filing date than patent A. Instead, an interference should be suggested.

Example 2

Two applications, C and D, with interfering claims are pending. Examination of application C is completed and all claims are allowable. Examination of application D is not completed. Application C should be issued promptly. If application C has an earlier effective U.S. filing date when issued as patent C, or when published as application publication C, it may be available as prior art under 35 U.S.C. 102(e) against application D. However, even if application C's effective filing date is later than application D's effective filing date, application C should issue. Until examination of application D is completed, it is not known whether application D should be in interference with application C, so suspension of application C will rarely, if ever, be justified.

Example 3

Two applications, E and F, with interfering claims are pending. Both are ready to issue. (Such ties should be extremely rare; suspensions must not be used to create such ties.) If the applications have their earliest effective filing dates within six months of each other, then an interference may be suggested. If, however, application E's earliest effective filing date is more than six months before application F's earliest effective filing date, then application E should issue. If application E (or the resulting patent E) is available as prior art (under 35 U.S.C. 102(a) or 102(e)) against application F, then a rejection should be made. If not, a requirement under 37 CFR 41.202(d) to show priority should be made. See MPEP § 2305.<

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2303.02 Other Outstanding Issues with Patents [R-4]

Patents that are undergoing reexamination or reissue are subject to the requirement of 37 CFR 41.102 that examination be completed. Patents may, however, be the subject of other proceedings before the Office. For instance, a patent may be the subject of a petition to accept a late maintenance fee, 35 U.S.C. 41(c), or a request for disclaimer or correction. 35 U.S.C. 253 to 256. Such issues must be resolved before an interference is suggested because they may affect whether or how an interference may be declared.

Example 1

A patent maintenance fee has not been timely paid. By operation of law, 35 U.S.C. 41(b), the patent is considered to be expired. An interference cannot be declared with an expired patent. 35 U.S.C. 135(a). Consequently, if a petition to accept delayed payment is not granted, 37 CFR 1.378, then no interference can be declared.

Example 2

A disclaimer under 35 U.S.C. 253, is filed for the sole patent claim directed to the same invention as the claims of the applicant. Since the patentee and applicant must both have claims to the same invention, 35 U.S.C. 102(g)(1), no interference can be declared.

Example 3

Similar to Example 2, a request for correction under 35 U.S.C. 254 or 255, is filed that results in a change to the sole patent claim such that it is no longer directed to the same invention as any claim of the applicant. Again, since the patentee and applicant must both have claims to the same invention, 35 U.S.C. 102(g)(1), no interference can be declared.

Example 4

Inventorship is corrected such that the inventors for the patent and the application are the same. Since 35 U.S.C. 102(g)(1) requires the interference to be with "another inventor," the correction eliminates the basis for an interference. Other rejections, such as a double-patenting rejection may be appropriate.<

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2304 Suggesting an Interference [R-4]

The suggestion for an interference may come from an applicant or from an examiner. Who suggests the interference determines what must be done and shown prior to declaration of an interference. In either circumstance, the examiner must consult with an Interference Practice Specialist (IPS), who may then refer the suggested interference to the Board of Patent Appeals and Interferences.<

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2304.01 Preliminaries to Referring an Interference to the Board [R-4]

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2304.01(a) Interference Search [R-4]

When an application is in condition for allowance, an interference search must be made by performing a text search of the "US-PGPUB" database in EAST or WEST directed to the comprehensive inventive features in the broadest claim. If the application contains a claim directed to a nucleotide or peptide sequence, the examiner must submit a request to STIC to perform an interference search of the sequence. If the search results identify any potential interfering subject matter, the examiner will review the application(s) with the potential interfering subject to determine whether interfering subject matter exists. If interfering subject matter does exist, the examiner will follow the guidance set forth in this chapter. If there is no interfering subject matter then the examiner should prepare the application for issuance. A printout of only the database(s) searched, the query(ies) used in the interference search, and the date the interference search was performed must be made of record in the application file. The results of the interference search must not be placed in the application file.

The search for interfering applications must not be limited to the class or subclass in which the application is classified, but must be extended to all classes, in and out of the Technology Center (TC), in which it has been necessary to search in the examination of the application. See MPEP § 1302.08.<

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2304.01(b) Obtaining Control Over Involved Files [R-4]

Ordinarily applications that are believed to interfere should be assigned to the same examiner.

I. IN DIFFERENT TECHNOLOGY CENTERS

If the interference would be between two applications, and the applications are assigned to different Technology Centers (TCs), then one application must be reassigned. Ordinarily the applications should both be assigned to the TC where the commonly claimed invention would be classified. After termination of the interference, further transfer may be appropriate depending on the outcome of the interference.

II. PAPERS NOT CONVERTED TO IMAGE FILE WRAPPER FILES

Although the official records for most applications have been converted into Image File Wrapper (IFW) files, some records exist only in paper form, particularly older benefit application files. Even IFW files may have artifact records that have not been converted. Complete patent and benefit files are necessary for determining whether benefit should be accorded for purposes of 35 U.S.C. 102(g)(1). A suggested interference must not be referred to the Board of Patent Appeals and Interferences (Board) if all files, including benefit files, are not available to the examiner in either IFW format or paper.

If a paper file wrapper has been lost, it must be reconstructed before the interference is referred to the Board.

III. PATENT COOPERATION TREATY APPLICATION FILES

Generally, a separate application file for a Patent Cooperation Treaty (PCT) application is not required for according benefit because the PCT application is included in a national stage application file that is itself either the application involved in the interference or a benefit file. Occasionally, however, the PCT application file itself is required for benefit. For instance, if benefit is claimed to the PCT application, but not to a national stage application in which it is included, then the PCT application file must be obtained.<

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2304.01(c) Translation of Foreign Benefit Application [R-4]

A certified translation of every foreign benefit application or Patent Cooperation Treaty (PCT) application not filed in English is required. 35 U.S.C. 119(b)(3) and 372(b)(3) and 37 CFR 1.55(a)(4). If no certified translation is in the official record for the application, the examiner must require the applicant to file a certified translation. The applicant should provide the required translation if applicant wants the application to be accorded benefit of the non-English language application. Any showing of priority that relies on a non-English language application is *prima facie* insufficient if no certified translation of the application is on file. 37 CFR 41.154(b) and 41.202(e).

Form paragraph 23.19 may be used to notify applicant that a certified English translation of the priority document is required.

¶ *23.19 Foreign Priority Not Substantiated*

Should applicant desire to obtain the benefit of foreign priority under 35 U.S.C. 119(a)-(d) prior to declaration of an interference, a certified English translation of the foreign application must be submitted in reply to this action, 37 CFR 41.154(b) and 41.202(e).

Failure to provide a certified translation may result in no benefit being accorded for the non-English application.

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2304.01(d) Sorting Claims [R-4]

An applicant may be entitled to a day-for-day patent term adjustment for any time spent in an interference. If an applicant has several related applications with interfering claims intermixed with claims that do not interfere, the examiner should consider whether the interfering claims should be consolidated in a single application or whether an application should be restricted to claims that do not interfere. This way examination can proceed for any claims that do not interfere without the delay that will result from the interference.

Interfering claims of an applicant are “conflicting claims” within the meaning of 37 CFR 1.78(b). The

examiner may require consolidation of such claims into any disclosure of the applicant that provides support for the claims. 35 U.S.C. 132(a).

Similarly, the examiner should require an applicant to restrict an application to the interfering claims, 35 U.S.C. 121, in which case the applicant may file a divisional application for the claims that do not interfere.

Sorting of claims may not be appropriate in all cases. For instance, a claim should not be consolidated into an application that does not provide support under 35 U.S.C. 112, first paragraph for the claim.<

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2304.02 Applicant Suggestion [R-4]

37 CFR 41.202. Suggesting an interference.

(a) *Applicant.* An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must:

(1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference,

(2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts,

(3) For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a),

(4) Explain in detail why the applicant will prevail on priority,

(5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification, and

(6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter.

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(d) *Requirement to show priority under 35 U.S.C. 102(g).* (1) When an applicant has an earliest constructive reduction to practice that is later than the apparent earliest constructive reduction to practice for a patent or published application claiming interfering subject matter, the applicant must show why it would prevail on priority.

(2) If an applicant fails to show priority under paragraph (d)(1) of this section, an administrative patent judge may nevertheless declare an interference to place the applicant under an order to show cause why judgment should not be entered against the applicant on priority. New evidence in support of priority will not be admitted except on a showing of good cause. The Board may authorize the filing of motions to redefine the interfering subject matter or to change the benefit accorded to the parties.

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When an applicant suggests an interference under 37 CFR 41.202(a), an examiner must review the suggestion for formal sufficiency. As explained in MPEP § 2304.02(c), the examiner is generally not responsible for determining the substantive adequacy of any priority showing. The examiner may, however, offer pertinent observations on any showing when the suggested interference is referred to the Board of Patent Appeals and Interferences. The observations may be included as an attachment to the Form PTO-850.

Form paragraphs 23.06 to 23.06.06 may be used to acknowledge applicant's suggestion for interference under 37 CFR 41.202(a) that failed to comply with one or more of paragraphs (a)(1) to (a)(6) of 37 CFR 41.202.

¶ *23.06 Applicant Suggesting an Interference*

Applicant has suggested an interference pursuant to 37 CFR 41.202(a) in a communication filed **[1]**.

Examiner Note:

1. Use this form paragraph if applicant has suggested an interference under 37 CFR 41.202(a) and applicant has failed to comply with one or more of paragraphs (a)(1) to (a)(6) of 37 CFR 41.202.

2. In bracket 1, insert the date of applicant's communication.

3. This form paragraph must be followed by one or more of form paragraphs 23.06.01 to 23.06.03 and end with form paragraph 23.06.04.

¶ *23.06.01 Failure to Identify the Other Application or Patent*

Applicant failed to provide sufficient information to identify the application or patent with which the applicant seeks an interference. See 37 CFR 41.202(a)(1) and MPEP § 2304.02(a).

¶ *23.06.02 Failure to Identify the Counts and Corresponding Claims*

Applicant failed to (1) identify all claims the applicant believes interfere, and/or (2) propose one or more counts, and/or (3) show how the claims correspond to one or more counts. See 37 CFR 41.202(a)(2) and MPEP § 2304.02(b).

¶ *23.06.03 Failure to Provide Claim Chart Comparing At Least One Claim*

Applicant failed to provide a claim chart comparing at least one claim of each party corresponding to the count. See 37 CFR 41.202(a)(3) and MPEP § 2304.02(c).

¶ *23.06.04 Failure to Explain in Detail Why Applicant Will Prevail on Priority*

Applicant failed to provide a detailed explanation as to why applicant will prevail on priority. See 37 CFR 41.202(a)(4), (a)(6), (d) and MPEP § 2304.02(c).

¶ *23.06.05 Claim Added/Amended; Failure to Provide Claim Chart Showing Written Description*

Claim **[1]** has been added or amended in a communication filed on **[2]** to provoke an interference. Applicant failed to provide a claim chart showing the written description for each claim in the applicant's specification. See 37 CFR 41.202(a)(5) and MPEP § 2304.02(d).

¶ *23.06.06 Time Period for Reply*

Applicant is given ONE MONTH or THIRTY DAYS, whichever is longer, from the mailing date of this communication to correct the deficiency(ies). THE PROVISIONS OF 37 CFR 1.136 DO **NOT** APPLY TO THE TIME SPECIFIED IN THIS ACTION.

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2304.02(a) Identifying the Other Application or Patent [R-4]

37 CFR 41.202. Suggesting an interference.

(a) *Applicant*. An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must:

(1) Provide sufficient information to identify the application or patent with which the applicant seeks an interference,

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Usually an applicant seeking an interference will know the application serial number or the patent number of the application or patent, respectively, with which it seeks an interference. If so, providing that number will fully meet the identification requirement of 37 CFR 41.202(a)(1).

Occasionally, an applicant will believe another interfering application exists based only on indirect evidence, for instance through a journal article, a "patent pending" notice, or a foreign published application. In such cases, information about likely named inventors and likely assignees may lead to the right application. The applicant should be motivated to help the examiner identify the application since inadequate information may prevent the declaration of the suggested interference.<

>

2304.02(b) Counts and Corresponding Claims [R-4]

37 CFR 41.202. Suggesting an interference.

(a) *Applicant*. An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must:

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(2) Identify all claims the applicant believes interfere, propose one or more counts, and show how the claims correspond to one or more counts,

(3) For each count, provide a claim chart comparing at least one claim of each party corresponding to the count and show why the claims interfere within the meaning of § 41.203(a),

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The applicant must identify at least one patentable claim from every application or patent that interferes for each count. A count is just a description of the interfering subject matter, which the Board of Patent Appeals and Interferences uses to determine what evidence may be used to prove priority under 35 U.S.C. 102(g)(1).

The examiner must confirm that the applicant has (A) identified at least one patentable count, (B) identified at least one patentable claim from each party for each count, and (C) has provided a claim chart comparing at least one set of claims for each count. The examiner need not agree with the applicant's suggestion. The examiner's role is to confirm that there are otherwise patentable interfering claims and that the formalities of 37 CFR 41.202 are met.<

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2304.02(c) Explaining Priority [R-4]

37 CFR 41.202. Suggesting an interference.

(a) *Applicant*. An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must:

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(4) Explain in detail why the applicant will prevail on priority,

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(6) For each constructive reduction to practice for which the applicant wishes to be accorded benefit, provide a chart showing where the disclosure provides a constructive reduction to practice within the scope of the interfering subject matter.

*****

(d) *Requirement to show priority under 35 U.S.C. 102(g)*. (1) When an applicant has an earliest constructive reduction to practice that is later than the apparent earliest constructive reduction to practice for a patent or published application claiming interfering subject matter, the applicant must show why it would prevail on priority.

(2) If an applicant fails to show priority under paragraph (d)(1) of this section, an administrative patent judge may never-

theless declare an interference to place the applicant under an order to show cause why judgment should not be entered against the applicant on priority. New evidence in support of priority will not be admitted except on a showing of good cause. The Board may authorize the filing of motions to redefine the interfering subject matter or to change the benefit accorded to the parties.

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A description in an application that would have anticipated the subject matter of a count is called a constructive reduction-to-practice of the count. One disclosed embodiment is enough to have anticipated the subject matter of the count. If the application is relying on a chain of benefit disclosures under any of 35 U.S.C. 119, 120, 121 and 365, then the anticipating disclosure must be continuously disclosed through the entire benefit chain or no benefit may be accorded.

If the application has an earlier constructive reduction-to-practice than the apparent earliest constructive reduction-to-practice of the other application or patent, then the applicant may simply explain its entitlement to its earlier constructive reduction-to-practice. Otherwise, the applicant must (A) antedate the earliest constructive reduction-to-practice of the other application or patent, (B) demonstrate why the other application or patent is not entitled to its apparent earliest constructive reduction-to-practice, or (C) provide some other reason why the applicant should be considered the prior inventor.

The showing of priority may look similar to showings under 37 CFR 1.130-1.132, although there are differences particularly in the scope of what must be shown. In any case, with the exception discussed below, the examiner is not responsible for examining the substantive sufficiency of the showing.

I. REJECTION UNDER 35 U.S.C. 102(a) or 102(e)

If an application claim is subject to a rejection under 35 U.S.C. 102(a) or 102(e) and the applicant files a suggestion under 37 CFR 41.202(a) rather than a declaration under 37 CFR 1.130-1.132, then the examiner must review the suggestion to verify that the applicant's showing, taken at face value, is sufficient to overcome the rejection. If the examiner determines that the showing is not sufficient, then the examination is not completed, 37 CFR 41.102, the rejection should be maintained and the suggestion should not be referred to the Board of Patent Appeals and Interferences (Board) for an interference.

II. COMPLIANCE WITH 35 U.S.C. 135(b)

If an application claim interferes with a claim of a patent or published application, and the claim was added to the application by an amendment filed more than one year after issuance of the patent, or the application was not filed until more than one year after issuance of the patent (but the patent is not a statutory bar), then under the provisions of 35 U.S.C. 135(b), an interference will not be declared unless at least one of the claims which were in the application, or in a parent application, prior to expiration of the one-year period was for "substantially the same subject matter" as at least one of the claims of the patent.

If the applicant does not appear to have had a claim for "substantially the same subject matter" as at least one of the patent claims prior to the expiration of the one-year period, the examiner may require, 35 U.S.C. 132, that the applicant explain how the requirements of 35 U.S.C. 135(b) are met. Further, if the patent issued from an application which was published under 35 U.S.C. 122(b), note the one year from publication date limitation found in 35 U.S.C. 135(b)(2) with respect to applications filed after the date of publication.

The obviousness test is not the standard for determining whether the subject matter is the same or substantially the same. Rather the determination turns on the presence or absence of a different material limitation in the claim. These tests are distinctly different. The analysis focuses on the interfering claim to determine whether all material limitations of the interfering claim necessarily occur in a prior claim. *In re Berger*, 279 F.3d 975, 61 USPQ2d 1523 (Fed. Cir. 2002). If none of the claims which were present in the application, or in a parent application, prior to expiration of the one-year period meets the "substantially the same subject matter" test, the interfering claim should be rejected under 35 U.S.C. 135(b). *In re McGrew*, 120 F.3d 1236, 43 USPQ2d 1632 (Fed. Cir. 1997). Note that the expression "prior to one year from the date on which the patent was granted" in 35 U.S.C. 135(b) includes the one-year anniversary date of the issuance of a patent. *Switzer v. Sockman*, 333 F.2d 935, 142 USPQ 226 (CCPA 1964).

Form paragraph 23.14 may be used to reject a claim as not being made prior to one year of the patent issue date. Form paragraph 23.14.01 may be used to reject a claim as not being made prior to one year from the application publication date.

¶ *23.14 Claims Not Copied Within One Year of Patent Issue Date*

Claim **[l]** rejected under 35 U.S.C. 135(b)(1) as not being made prior to one year from the date on which U.S. Patent No. **[2]** was granted. See *In re McGrew*, 120 F.3d 1236, 1238, 43 USPQ2d 1632, 1635 (Fed. Cir. 1997) where the Court held that 35 U.S.C. 135(b) may be used as a basis for *ex parte* rejections.

¶ *23.14.01 Claims Not Copied Within One Year Of Application Publication Date*

Claim **[l]** rejected under 35 U.S.C. 135(b)(2) as not being made prior to one year from the date on which **[2]** was published under 35 U.S.C. 122(b). See *In re McGrew*, 120 F.3d 1236, 1238, 43 USPQ2d 1632, 1635 (Fed. Cir. 1997) where the Court held that 35 U.S.C. 135(b) may be used as a basis for *ex parte* rejections.

Examiner Note:

1. In bracket 2, insert the publication number of the published application.

2. This form paragraph should only be used if the application being examined was filed after the publication date of the published application.

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2304.02(d) Adequate Written Description [R-4]

37 CFR 41.202. Suggesting an interference.

(a) *Applicant*. An applicant, including a reissue applicant, may suggest an interference with another application or a patent. The suggestion must:

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(5) If a claim has been added or amended to provoke an interference, provide a claim chart showing the written description for each claim in the applicant's specification, and

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An applicant is not entitled to an interference simply because applicant wants one. The interfering claim must be allowable, particularly with respect to the written description supporting the interfering claim.

Historically, an applicant provoked an interference by copying a claim from its opponent. The problem this practice created was that differences in the underlying disclosures might leave the claim allowable to one party, but not to the other; or despite identical claim language differences in the disclosures might require that the claims be construed differently.

Rather than copy a claim literally, the better practice is to add (or amend to create) a fully supported claim and then explain why, despite any apparent differences, the claims define the same invention. 37 CFR 41.203(a). The problem of inadequate written description in claims added or amended to provoke an interference is so great that the issue has been singled out for heightened scrutiny early in the course of an interference. 37 CFR 41.201, under "Threshold issue."<

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2304.03 Patentee Suggestion [R-4]

37 CFR 41.202. Suggesting an interference.

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(b) Patentee. A patentee cannot suggest an interference under this section but may, to the extent permitted under § 1.99 and § 1.291 of this title, alert the examiner of an application claiming interfering subject matter to the possibility of an interference.

*****

A patentee may not suggest an interference unless it becomes an applicant by filing a reissue application. A patentee may, however, to the limited extent permitted under 37 CFR 1.99 and 1.291, alert an examiner to the existence of interfering claims in an application. See MPEP § 1134 and § 1901.<

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2304.04 Examiner Suggestion [R-4]

37 CFR 41.202. Suggesting an interference.

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(c) *Examiner*. An examiner may require an applicant to add a claim to provoke an interference. Failure to satisfy the requirement within a period (not less than one month) the examiner sets will operate as a concession of priority for the subject matter of the claim. If the interference would be with a patent, the applicant must also comply with paragraphs (a)(2) through (a)(6) of this section. The claim the examiner proposes to have added must, apart from the question of priority under 35 U.S.C. 102 (g):

(1) Be patentable to the applicant, and

(2) Be drawn to patentable subject matter claimed by another applicant or patentee.

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2304.04(a) Interfering Claim Already in Application [R-4]

If the applicant already has a claim to the same subject matter as a claim in the application or patent of another inventor, then there is no need to require the applicant to add a claim to have a basis for an interference.

The examiner may invite the applicant to suggest an interference pursuant to 37 CFR 41.202(a). An applicant may be motivated to do so in order to present its views on how the interference should be declared.

If the applicant does not suggest an interference, then the examiner should work with an Interference Practice Specialist (IPS) to suggest an interference to the Board of Patent Appeals and Interferences (Board). The suggestion should include an explanation of why at least one claim of every application or patent defines the same invention within the meaning of 37 CFR 41.203(a). See MPEP § 2301.03 for a discussion of interfering subject matter. The examiner must also complete Form PTO-850.

The examiner should be prepared to discuss why claims interfere, whether the subject matter of other claims would have been anticipated or rendered obvious if the interfering claims are treated as prior art, and whether an applicant or patentee is entitled to claim the benefit of an application as a constructive reduction-to-practice. The IPS may require the examiner to prepare a memorandum for the Board on any of these subjects. The IPS may require the examiner to participate in a conference with the Board to discuss the suggested interference.<

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2304.04(b) Requiring a Claim [R-4]

35 U.S.C. 132. Notice of rejection; reexamination.

(a) Whenever, on examination, any claim for a patent is rejected, or any objection or requirement made, the Director shall notify the applicant thereof, stating the reasons for such rejection, or objection or requirement, together with such information and references as may be useful in judging of the propriety of continuing the prosecution of his application; and if after receiving such notice, the applicant persists in his claim for a patent, with or without amendment, the application shall be reexamined. No amendment shall introduce new matter into the disclosure of the invention.

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The examiner may, pursuant to 35 U.S.C. 132(a), require an applicant to add a claim that would interfere with the claim of another application or patent. For example, the requirement may be made to obtain a clearer definition of the interfering subject matter or to establish whether the applicant will pursue claims to the interfering subject matter. When the requirement is based on a published application with allowed claims or a patent, the examiner must identify the published application or the patent in making the requirement.

Given the cost and complexity of interferences, a requirement to add a claim under 37 CFR 41.202(c) should not be lightly made. Before making the requirement, the examiner should consult with an Interference Practice Specialist (IPS). The following principles should guide the examiner in exercising discretion to make this requirement:

(A) An interference should generally not be suggested if examination of the application is not otherwise completed.

(B) The required claim must not encompass prior art or otherwise be barred.

(C) The application must provide adequate support under 35 U.S.C. 112, first paragraph for the subject matter of the required claim.

(D) A claim should not be required when the applicant expressly states that the commonly described subject matter is not the applicant's invention.

(E) A claim based on a claim from a published application should not be required unless the claim from the published application has been allowed.

Example 1

A patent is 35 U.S.C. 102(b) prior art against any possible interfering claim. No interfering claim should be required.

Example 2

The patent issued more than one year ago and the applicant did not previously have a claim to the

same subject matter. Any added claim would most likely be time barred under 35 U.S.C. 135(b)(1). No interfering claim should be required.

Example 3

An application describes work that attributes to another inventor, but also describes and claims an improvement. The other inventor has received a patent for original work. The applicant may in some sense have 35 U.S.C. 112, first paragraph support for an interfering claim to the other inventor's work. Nevertheless, the applicant has indicated that the commonly described subject matter is not the applicant's invention. No interfering claim should be required.

Example 4

An application has support for both a generic claim G and a species claim G1. The applicant only claims the genus G. A patent discloses and claims only G1. Under the facts of this example, there is no evidence that genus G would have rendered the species G1 obvious. If for some reason the patent is not available as a reference against the application, the examiner may require the applicant to add a claim to species G1 after consulting with an IPS.

Example 5

Published application H and application I both support a claim to H1. Published application H contains a claim to H1, but application I does not. The claim to H1 in the published application is under rejection. Applicant I should not ordinarily be required to add the claim.

Form paragraph 23.04 may be used to require applicant to add a claim to provoke interference.

¶ *23.04 Requiring Applicant to Add Claim to Provoke Interference*

The following allowable claim from **[1]**is required to be added for the purpose of an interference:

[2]

The claim must be copied exactly.

Applicant is given ONE MONTH or THIRTY DAYS, whichever is longer, from the mailing date of this communication to add the claim. Refusal to add a required claim will operate as a concession of priority for the subject matter of the required claim, but will **not** result in abandonment of this application. See 37 CFR 41.202(c) and MPEP § 2304.04(b). THE PROVISIONS OF 37 CFR 1.136 DO NOT APPLY TO THE TIME SPECIFIED IN THIS ACTION.

If the interference would be with a patent, applicant must also comply with 37 CFR 41.202(a)(2) to (a)(6).

Examiner Note:

1. In bracket 1, insert the published application number if the claim is an allowed claim from a U.S. application publication or the patent number if the claim is from a U.S. patent.
2. In bracket 2, insert the claim which applicant is required to add to provoke an interference.

APPLICANT MUST ADD THE CLAIM

If required to add a claim under 37 CFR 41.202(c), the applicant must do so. Refusal to add a required claim will operate as a concession of priority for the subject matter of the required claim. The applicant would then be barred from claiming, not only the subject matter of the required claim, but any subject matter that would have been anticipated or rendered obvious if the required claim were treated as prior art. *In re Ogiue*, 517 F.2d 1382, 1390, 186 USPQ 227, 235 (CCPA 1975).

While complying with the requirement to add a claim, an applicant may also express disagreement with the requirement several ways, including:

(A) Identifying a claim already in its application, or another of its applications, that provides a basis for the proposed interference;

(B) Adding an alternative claim and explaining why it would provide a better basis for the proposed interference (such as having better support in the applicant's disclosure); or

(C) Explaining why the required claim is not patentable to the applicant.

The examiner may withdraw the requirement if persuaded by the reasons the applicant offers.<

>

2304.05 Common Ownership [R-4]

37 CFR 41.206. Common interests in the invention.

An administrative patent judge may decline to declare, or if already declar ed the Board may issue judgment in, an interference between an application and another application or patent that are commonly owned.

An interference is rarely appropriate between two applications or an application and patent that belong to the same owner. The owner should ordinarily be able to determine priority and is obligated under 37 CFR 1.56 to inform the examiner about which application or patent is entitled to priority. The examiner

may require an election of priority between the application and other application or patent. 35 U.S.C. 132(a).

In making the election, the owner must eliminate the commonly claimed subject matter. This may be accomplished by canceling the interfering application claims, disclaiming the interfering patent claims, amending the application claims such that they no longer interfere, or filing a reissue application to amend the patent claims such that they no longer interfere.

Example 1

Two corporations have applications that claim the same invention. After a merger of the corporations, the resulting corporation owns both applications. The new corporation is obligated to investigate priority. Once the corporation has had an opportunity to determine which application is entitled to priority, the corporation must elect between the applications or otherwise eliminate the need for an interference.

Example 2

J files an application in which J is the sole inventor and assignee. K files an application in which J and K are named as inventors and co-assignees. Although J is an owner of both applications, an interference may nevertheless be necessary if J and K disagree about which application is entitled to priority.<

>

2305 Requiring a Priority Showing [R-4]

37 CFR 41.202. Suggesting an interference.

*****

(d) *Requirement to show priority under 35 U.S.C. 102(g).* (1) When an applicant has an earliest constructive reduction to practice that is later than the apparent earliest constructive reduction to practice for a patent or published application claiming interfering subject matter, the applicant must show why it would prevail on priority.

*****

(e) *Sufficiency of showing.* (1) A showing of priority under this section is not sufficient unless it would, if unrebutted, support a determination of priority in favor of the party making the showing.

(2) When testimony or production necessary to show priority is not available without authorization under § 41.150(c) or § 41.156(a), the showing shall include:

(i) Any necessary interrogatory, request for admission, request for production, or deposition request, and

(ii) A detailed proffer of what the response to the interrogatory or request would be expected to be and an explanation of the relevance of the response to the question of priority.

*****

Whenever the application has an earliest constructive reduction-to-practice that is later than the earliest constructive reduction-to-practice of a published application having allowed claims or a patent with which it interferes, the applicant must make a priority showing under 37 CFR 41.202(d)(1).

There are two typical situations in which a showing under 37 CFR 41.202(d)(1) is filed without a requirement from the examiner. First, the applicant may be complying with 37 CFR 41.202(a)(2) in order to suggest an interference under 37 CFR 41.202(a) or as part of complying with a requirement under 37 CFR 41.202(c). Second, the applicant may file the showing to overcome a rejection based on 35 U.S.C. 102(a) or 102(e) when an affidavit is not permitted under 37 CFR 1.131(a)(1) because the applicant is claiming interfering subject matter.

If no showing has been filed, and the application's earliest constructive reduction-to-practice is later than the earliest constructive reduction-to-practice of a patent or published application, then the examiner must require a showing of priority. This showing is necessary because an insufficient showing (including no showing at all) can trigger a prompt judgment against the applicant in an interference. 37 CFR 41.202(d)(2). The applicant may choose to comply with a requirement under 37 CFR 41.202(d)(1) by suggesting an interference under 37 CFR 41.202(a).

Example

Application L has claims that interfere with claims of patent M. Application L was filed in June 2001. The application that resulted in patent M was filed in November 2001, but has an earliest constructive reduction-to-practice in a foreign application filed in December 2000. Assuming no rejection is available under 35 U.S.C. 102(e), the examiner must require a showing under 37 CFR 41.202(d)(1) in application L.

I. RELATIONSHIP TO 37 CFR 1.131 AFFIDAVIT

Ordinarily an applicant may use an affidavit of prior invention under 37 CFR 1.131 to overcome a rejection under 35 U.S.C. 102(a) or 102(e). An exception to the rule arises when the reference is a patent or application published under 35 U.S.C. 122(b) and the reference has claims directed to the same patentable invention as the application claims being rejected. 37 CFR 1.131(a)(1). The reason for this exception is that priority is determined in an interference when the claims interfere. 35 U.S.C. 135(a). In such a case, the applicant must make the priority showing under 37 CFR 41.202(d) instead. In determining whether a 37 CFR 1.131 affidavit is permitted or not, the examiner should keep the purpose of the exception in mind. If an interference would not be possible at the time the affidavit would be submitted, then the affidavit should be permitted. This situation could arise two ways.

First, the claims that matter for the purposes of 37 CFR 1.131 are not the published claims but the currently existing claims. For example, if the claims that were published in a published application have been significantly modified during subsequent examination, they may no longer interfere with the rejected claims. Similarly, the patent claims may have been subsequently corrected or amended in a reissue application or a reexamination. Since an interference no longer exists between the current claims in the patent or published application and the rejected claims, an affidavit under 37 CFR 1.131 may be submitted.

Similarly, if a published application contains claims to the same invention, but the claims in the published application are not in condition for allowance, then no interference is yet possible. 37 CFR 41.102. Since the claims in the published application might never be allowed in their present form, it is not appropriate to proceed as though an interference would be inevitable. Consequently, an affidavit under 37 CFR 1.131 may be submitted.

II. NOT A PRIORITY STATEMENT

A priority showing under 37 CFR 41.202(d)(1), which is presented during examination, is not the same as a priority statement under 37 CFR 41.204(a), which is filed during an interference. A priority statement is a notice of what a party intends to prove on the issue of priority during an interference. A priority showing under 37 CFR 41.202(d)(1) must, however, actually prove priority assuming that the opposing party did not oppose the showing. 37 CFR 41.202(e)(1). Generally speaking, while a priority statement might be more detailed in some respects, it will not be sufficient to make the necessary showing of priority for the purposes of 37 CFR 41.202.

An applicant presenting a priority showing must establish through the showing that it would prevail on priority if an interference is declared and the opponent does not oppose the showing. The requirement for a priority showing is intended to spare a senior party patentee the burden of an interference if the junior party applicant cannot establish that it would prevail in an interference even if the senior party does nothing. *Kistler v. Weber*, 412 F.2d 280, 283-85, 162 USPQ 214, 217-19 (CCPA 1969) and *Edwards v. Strazzabosco*, 58 USPQ2d 1836 (Bd. Pat. App. & Inter. 2001).

The consequence of an inadequate showing may be serious for the applicant. If an interference is declared and the Board of Patent Appeals and Interferences (Board) finds the priority showing insufficient (thereby issuing an order to show cause why judgment should not be entered against the applicant), the applicant will not be allowed to present additional evidence to make out a priority showing unless the applicant can show good cause why any additional evidence was not presented in the first instance with the priority showing before the examiner. 37 CFR 41.202(d)(2); *Huston v. Ladner*, 973 F.2d 1564, 23 USPQ2d 1910 (Fed. Cir. 1992); *Hahn v. Wong*, 892 F.2d 1028, 13 USPQ2d 1313 (Fed. Cir. 1989); *Edwards v. Strazzabosco*, 58 USPQ2d 1836 (Bd. Pat. App. & Inter. 2001). The principles which govern review of a priority showing are discussed in *Basmadjian v. Landry*, 54 USPQ2d 1617 (Bd. Pat. App. & Inter. 1997) (citing former 37 CFR 1.608(b)).<

>

2306 Secrecy Order Cases [R-4]

37 CFR 5.3. Prosecution of application under secrecy orders; withholding patent.

*****

(b) An interference will not be declared involving a national application under secrecy order. An applicant whose application is under secrecy order may suggest an interference (§ 41.202(a) of

this title), but the Office will not act on the request while the application remains under a secrecy order.

*****

Once an interference is declared, an opposing party is entitled to access to the application and benefit applications. 37 CFR 41.109. See MPEP § 2307.02. Consequently, an interference should not be suggested for an application under a secrecy order. See MPEP § 120 and § 130. When a secrecy order expires or is rescinded, if the examination is otherwise completed, 37 CFR 41.102, then the need for an interference may be reconsidered.

If an application not under a secrecy order has allowable claims that interfere with allowable claims of an application that is under a secrecy order, then the application that is not under the secrecy order should be passed to issue as a patent. An interference may be suggested with the application and the patent (unless the patent has expired) once the secrecy order has been lifted.

Example

Application L discloses and claims a transistor that is useful in a commercial context. Application M discloses the same transistor in the context of a missile control circuit, but claims only the transistor. A secrecy order is placed on application M. Once examination of application L is completed and the transistor claim is allowable, application L should pass to issue.<

>

2307 Action During an Interference [R-4]

37 CFR 41.103. Jurisdiction over involved files.

The Board acquires jurisdiction over any involved file when the Board initiates a contested case. Other proceedings for the involved file within the Office are suspended except as the Board may order.

Once a patent or application becomes involved in an interference, the Board of Patent Appeals and Interferences (Board) has jurisdiction over the file. The examiner may not act on an involved patent or application except as the Board may authorize.

The Board may occasionally consult with the examiner, for instance, on a question regarding the technology at issue in an involved application or patent.

The Board retains jurisdiction over the interference until the interference is terminated. The Director has defined termination to occur after a final Board judgment in the interference and the period for seeking judicial review has expired or, if judicial review is sought, after completion of judicial review including any further action by the Board. 37 CFR 41.205(a).<

>

2307.01 *Ex Parte* Communications [R-4]

37 CFR 41.11. Ex parte communications in inter partes proceedings.

An ex parte communication about an inter partes reexamination (subpart C of this part) or about a contested case (subparts D and E of this part) with a Board member, or with a Board employee assigned to the proceeding, is not permitted.

Since an interference involves two or more parties, the integrity of the process requires the opportunity for the opposing party to participate in communications or actions regarding any involved application or patent. Once an interference is declared, any attempt by a party to communicate with the Board of Patent Appeals and Interferences (Board) through the examiner or to have the examiner act in an involved patent or application without Board authorization should be promptly reported to the Board. Board action may include a sanction in the interference or referral of a patent practitioner to the Office of Enrollment and Discipline.<

>

2307.02 Access to Related Files [R-4]

37 CFR 41.109. Access to and copies of Office records.

(a) *Request for access or copies*. Any request from a party for access to or copies of Office records directly related to a contested case must be filed with the Board. The request must precisely identify the records and in the case of copies include the appropriate fee set under § 1.19(b) of this title.

(b) *Authorization of access and copies.* Access and copies will ordinarily only be authorized for the following records:

(1) The application file for an involved patent;

(2) An involved application; and

(3) An application for which a party has been accorded benefit under subpart E of this part.

*****

In addition to any access permitted to a member of the public under 37 CFR 1.11 and 1.14 (see MPEP § 103), an opposing party may be authorized under 37 CFR 41.109 to have access to or a copy of the record for any involved patent or application, and for any

application for which benefit has been accorded. The availability of a file to an opposing party under 37 CFR 41.109 has no bearing on whether a file is otherwise available under 37 CFR 1.11 or 1.14.<

>

2307.03 Suspension of Related Examinations [R-4]

Although the examiner may not act in a patent or an application directly involved in an interference, 37 CFR 41.103, examination may continue in related cases, including any benefit files. Once examination is completed, the examiner should consult with an Interference Practice Specialist (IPS) to determine whether and how further action should proceed. The IPS may consult with the Board of Patent Appeals and Interferences (Board) to determine whether the application claims would be barred in the event the applicant loses the interference.

Suspension may be necessary if the claims would be barred by a loss in the interference. Steps should be considered to minimize the effect of any patent term adjustment that would result from the suspension. For instance, the examiner could require restriction, 35 U.S.C. 121, of the application to only the claims that do not interfere so that they can be issued. The applicant may then file a divisional application with the interfering claims, which may be suspended.<

>

2307.04 Additional Parties to Interference [R-4]

During the course of an interference, the examiner may come across applications or patents of parties that claim the same invention, but are not already involved in the interference. If so, the examiner should consult with an Interference Practice Specialist (IPS) and prepare a referral of the suggested interference to the Board of Patent Appeals and Interferences in the same way that a referral is prepared in the first instance.<

>

2307.05 Board Action on Related Files [R-4]

Occasionally, the Board may order that a paper be filed in a related application. Generally, the paper will notify the examiner of a fact, such as a party admission or prior art, that may be relevant to examination of the related case.<

>

2307.06 Action at the Board [R-4]

Action at the Board of Patent Appeals and Interferences (Board) during an interference is beyond the scope of this Chapter. For further information, see 37 CFR part 41, subparts A, D, and E; see also the Board's Contested Case Practice Guide. A Standing Order and other orders, which further direct the conduct of the parties, are also entered in each interference.<

>

2308 Action After an Interference [R-4]

37 CFR 41.127. Judgment.

(a) *Effect within Office*—(1) *Estoppel*. A judgment disposes of all issues that were, or by motion could have properly been, raised and decided. A losing party who could have properly moved for relief on an issue, but did not so move, may not take action in the Office after the judgment that is inconsistent with that party's failure to move, except that a losing party shall not be estopped with respect to any contested subject matter for which that party was awarded a favorable judgment.

(2) *Final disposal of claim*. Adverse judgment against a claim is a final action of the Office requiring no further action by the Office to dispose of the claim permanently.

*****

(c) *Recommendation*. The judgment may include a recommendation for further action by the examiner or by the Director. If the Board recommends rejection of a claim of an involved application, the examiner must enter and maintain the recommended rejection unless an amendment or showing of facts not previously of record is filed which, in the opinion of the examiner, overcomes the recommended rejection.

*****

Jurisdiction over an application returns to the examiner once the interference has terminated. If there is a recommendation for further action in the application, the examiner must reopen prosecution to consider the recommendation. The examiner must enter any recommended rejection, and must maintain the rejection unless the applicant by amendment or submission of new evidence overcomes the rejection to the examiner's satisfaction.

If there is no recommendation in the judgment, the examiner should update the search and may, but is not

required to, reopen prosecution for any claim not disposed of in the judgment.

An interference judgment simply resolves any question of priority between the two parties to the interference. The judgment does not prevent the examiner from making a rejection in further examination in the same application or a different application. If a party loses on an issue in the interference, the examiner should reject any claim for which allowance would be inconsistent with the interference judgment.

Form paragraph 23.02 may be used to resume *ex parte* prosecution.

¶ *23.02 Ex Parte Prosecution Is Resumed*

Interference No. **[1]** has been terminated by a decision **[2]** to applicant. *Ex parte* prosecution is resumed.

Examiner Note:

1. In bracket 1, insert the interference number.
2. In bracket 2, insert whether favorable or unfavorable.

<

>

2308.01 Final Disposal of Claims [R-4]

Judgment against a claim in an interference, including any judgment on priority or patentability, finally disposes of the claim. No further action is needed from the examiner on that claim. If no claim remains allowable to the applicant, a notice of abandonment should be issued.<

>

2308.02 Added or Amended Claims [R-4]

An applicant may file a motion during the interference to add or amend a claim. A patentee may file a reissue application in support of a motion to add or amend a claim. A copy of the paper adding or amending the claim will be placed in the official record of the application, but not entered. A decision on the motion is entered in the official record of the application. The examiner may enter the added claim or amended claim into the application only if, and only to the extent, authorized by the Board of Patent Appeals and Interferences, typically in the decision on the motion. The decision authorizing entry of the added or amended claim does not prevent the examiner from rejecting the claim during further prosecution.<

>

2308.03 Estoppel Within the Office [R-4]

If a party loses on an issue, it may not re-litigate the issue before the examiner or in a subsequent Board of Patent Appeals and Interferences (Board) proceeding. The time for the party to make all pertinent arguments is during the interference, unless the Board expressly prevented the party from litigating the issue during the interference.

There are two main types of interference estoppel. First, a losing party is barred on the merits from seeking a claim that would have been anticipated or rendered obvious by the subject matter of the lost count. *In re Deckler*, 977 F.2d 1449, 24 USPQ2d 1448 (Fed. Cir. 1992); *Ex parte Tytgat*, 225 USPQ 907 (Bd. Pat. App. & Inter. 1985). Second, a losing party is procedurally barred from seeking from the examiner relief that could have been--but was not--sought in the interference. 37 CFR 41.127(a)(1); *Ex parte Kimura*, 55 USPQ2d 1537 (Bd. Pat. App. & Inter. 2000) (reissue applicant estopped to claim compound when patentability of that compound could have been put in issue in interference where opponent's application also described compound).

The examiner should consult with an Interference Practice Specialist (IPS) before allowing a claim to a losing party that was added or amended during post-interference examination.

Example 1

The applicant lost on priority for a count drawn to subject matter X. The Board's judgment automatically disposed of all of the applicant's claims corresponding to the count. The applicant files a continuing application with a claim to subject matter X. The claim must be rejected as estopped on the merits by the applicant's loss in the interference.

Example 2

Same facts as Example 1 except the applicant files a continuing application with a claim generic to subject matter X. Since the generic claim encompasses subject matter lost in the interference, the generic claim must be rejected as estopped on the merits by the loss in the interference.

Example 3

Same facts as Example 1 except the applicant files a continuing application with a claim to subject matter that would have been obvious in view of subject matter X. The claim must be rejected as estopped on the merits by the applicant's loss in the interference, but the examiner must demonstrate why the claim would have been obvious if subject matter X is assumed to be prior art.

Example 4

Same facts as Example 1 except the applicant files a continuing application with a claim identical to a claim that corresponded to the count of the interference. The applicant also files a showing of why the claim should not have corresponded to the count. The claim should be rejected as procedurally estopped. Whether the showing is adequate or not, it is too late. The time to make the showing was during the interference.

Example 5

Same facts as Example 4 except that during the interference the applicant timely requested, but was not permitted, to show the claim did not correspond to the count. The examiner may determine in light of the new showing whether the lost count would have anticipated or rendered obvious the subject matter of the claim. The procedural estoppel does not apply if, through no fault of the applicant, the Board prevented the applicant from seeking relief during the interference.

Example 6

The applicant's claim 1 was held unpatentable during the interference. The applicant could have moved, but did not move, to amend the claim. The applicant files a continuing application with an amended claim 1. If the subject matter of the amended claim would have been anticipated or obvious in view of a count of the interference, it must be rejected as procedurally estopped. Whether the amendment is sufficient to overcome the ground for unpatentability or not, the time to have amended the claim was during the interference.

Example 7

Same situation as Example 6 except the applicant did move to amend the claim, but the motion was denied. The result is the same as in Example 6. If the subject matter of the amended claim would have been anticipated or obvious in view of a count of the interference, it must be rejected as procedurally estopped. The applicant's lack of success on the motion does not prevent the estoppel from applying to the claim.

Example 8

Same facts as Example 6 except the applicant filed a late request during the interference to amend the claim to overcome the basis for unpatentability. The request was denied as untimely. The claim must be rejected as procedurally estopped. Even though the applicant was not permitted to amend the claim during the interference, the estoppel still applies because the applicant's inability to obtain relief in the interference was the result of the applicant's failure to seek timely relief.<

>

2308.03(a) Losing Party [R-4]

A party is barred (estopped) from raising an issue if the party lost on the issue during the interference. A party may lose on one issue, yet not lose on a different issue.

Example

The applicant lost the interference on a count drawn to a compound, but the opponent lost on a count drawn to methods of using the compound. The applicant may continue to pursue claims to the method of using the compound, but not claims to the compound itself.<

>

2308.03(b) No Interference-in-Fact [R-4]

A judgment of no interference-in-fact means that no interference is needed to resolve priority between the parties. Neither party has lost the interference for the purpose of estoppel, 37 CFR 41.127(a)(1), even if one of the parties suggested the interference.

A judgment of no interference-in-fact bars any further interference between the same parties for claims to the same invention as the count of the interference.<

>

2308.03(c) No Second Interference [R-4]

No second interference should occur between the same parties on patentably indistinct subject matter. If the Board of Patent Appeals and Interferences held that there is no interference-in-fact between the parties for the subject matter of the count, that holding may not be reopened in further examination. If a party that lost the earlier interference is again claiming the same invention as the count, the interfering claims should be rejected as estopped.<

>

2309 National Aeronautics and Space Administration or Department of Energy [R-4]

Ownership of an invention made pursuant to a U.S. government contract may be vested in the contracting government agency. The Board of Patent Appeals and Interferences (Board) determines two such ownership contests using interference procedures: for the National Aeronautics and Space Administration (NASA), 42 U.S.C. 2457 (inventions having significant utility in aeronautical or space activity), and for the Department of Energy (DoE), 42 U.S.C. 2182 (inventions relating to special nuclear material or atomic energy).

An applicant with an application covered by these Acts must file a statement regarding the making or conception of the invention and any relation to a contract with NASA or DoE. See MPEP § 150 and § 151. The examiner should work in coordination with Licensing and Review and one of the Technology Centers Interference Practice Specialists in suggesting these cases to the Board. Although these cases are not interferences, the interference practices in this chapter generally apply to NASA and DoE ownership contests as well.<

●●●●●●●●●●●●●●●●●●●●●●●●●●●●

EXHIBIT L TO
PRINSTON PHARMACEUTICAL, INC.'S ANSWER TO FIRST AMENDED COMPLAINT FOR PATENT INFRINGEMENT AND COUNTERCLAIMS

REMARKS

Reconsideration of this application is requested. Claims 1-6 and 14, 17 and 18 are in the case. Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached pages are is captioned "**Version With Markings To Show Changes Made**."

I. SPECIFICATION

The Examiner has requested an amplified Abstract. In response, a new Abstract is presented on a separate sheet attached to this response in which the general formula of the claimed compounds is depicted.

The specification has been amended to indicate that the present application is a 371 National Phase application of PCT International Application PCT/SE99/02256, filed December 2, 1999.

II. THE FORMAL REJECTIONS

Claim 18 stands rejected as including compounds not within the scope of the compounds for formula (I). In response, Claim 18 has been amended to delete such compounds. The deleted compounds have been removed without

prejudice to the possibility of pursuing patent protection for those compounds in a separate continuing application.

Claims 1 and 5 stand rejected under 35 U.S.C. 112, second paragraph, on the ground that it is allegedly unclear what the language "or solvate thereof" is unclear. This rejection is respectfully traversed.

It is believed that a person of ordinary skill in this art would have no difficulty in understanding what is meant by "or solvate thereof" in the context of the presently claimed invention. For example, as noted at page 13, line 12, the solvate may be water, ethanol, tetrahydrofuran or diethyl ether. Reconsideration of this rejection is accordingly respectfully requested.

The Examiner has inquired as to the purpose of the proviso appearing at the end of Claim 1. The claimed invention of the present application is an improvement over the disclosure of U.S. Patent No. 6,251,910, issued June 26, 2001. A copy of that patent accompanies the present response, together with a completed PTO-1449 and an IDS fee. It is respectfully requested that the Examiner initial the attached PTO-1449 and return a copy of the initialed document to the undersigned as an indication that the attached patent has been considered and made of record in the present application.

As will be evident from the attached Declaration by two of the named Applicants in this case, namely Anthony H. Ingell and Brian Springthorpe, of the nine compounds exemplified in the present application, five were synthesized prior to the September 21, 1998 102(e) date of U.S. Patent No. 6,251,910. The utility is demonstrated in the specification (pages 13-16; 42-43). The attached Declaration is accompanied by copies of laboratory notebook pages of research chemists working under the direct supervision and control of the co-declarants.

In light of this, it is clear that U.S. Patent No. 6,251,910 is not available as prior art under 35 U.S.C. 102(e) against the presently claimed invention. No obvious rejection lies in this case.

Withdrawal of the outstanding formal rejections is now believed to be in order. Such action is respectfully requested.

III. THE OBVIOUSNESS REJECTION

Claim 1 stands rejected under rejected under 35 U.S.C. 103(a) in view of the presence of the proviso at the end of Claim 1. For the reasons discussed above, the obviousness rejection no longer stands in this case in light of the attached Declaration evidence. Reconsideration and withdrawal of the outstanding obviousness rejection are accordingly respectfully requested.

IV. THE 35 U.S.C. 101 REJECTION

Claims 7-13 have been rejected as being directed to a "use." In response, and without conceding the merit of this rejection, Claims 7-13 have been canceled without prejudice to the possibility of pursuing that subject matter in a separate continuing application.

Withdrawal of the outstanding 35 U.S.C. 101 rejection is now believed to be in order. Such action is respectfully requested.

V. THE 35 U.S.C. 112, FIRST PARAGRAPH, REJECTION

Claims 14-16 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly too broadly claimed on the ground that "prevention" is "very difficult to show." This rejection is respectfully traversed.

A person of ordinary skill in this art would have no difficulty in carrying out the method as claimed in respect of "prevention" of the recited conditions. Persons of ordinary skill in this art are well acquainted with techniques employed in preventative medicine, to achieve prophylaxis in patients susceptible to

disease. Reconsideration and withdrawal of this formal rejection are accordingly respectfully requested.

VI. RESTRICTION

The Examiner has asserted that Applicants are not entitled to more than one method of treatment cliamed. The Examiner has requested that Applicants "pick one believable utility they can demonstrate." In response, the method of Claim 14 is elected with traverse. Claims 15 and 16 have been canceled without prejudice to presenting that subject matter in a separate continuing case

Allowance of this application is awaited.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____

Leonard C. Mitchard
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Attachments: Executed Declaration; USP 6251910; PTO-1449; IDS Fee of $180

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

HARDERN et al

Serial No. **09/508,195**

Filed: **March 8, 2000**

For: **NOVEL COMPOUNDS**

Atty. Ref.: **3764-2**

Group: **1624**

Examiner: **Ford, J.**

* *

Honorable Commissioner of
Patents and Trademarks
Washington, DC 20231

DECLARATION

Sir:

We, Anthony H. Ingall and Brian Springthorpe, do hereby declare and state as follows:

1. Anthony H. Ingall:

My current job title with AstraZeneca UK Limited is "Associate Principal Scientist". I have been employed by AstraZeneca UK Limited and its predecessor companies for 26 years and, during all of that time, I have worked in the Department of Medicinal Chemistry primarily as a laboratory worker and supervisor of laboratory workers, but I also have certain administrative duties. At the time of the work in question, I directed a team of 5 people. I received my undergraduate degree from Imperial College, University of London, England in 1970 and my PhD also from Imperial College in 1973. My technical expertise is in the field of medicinal chemistry and synthetic organic chemistry.

2. Brian Springthorpe:

My position within AstraZeneca UK Limited is "Team Leader Medicinal Chemistry, AZ Charnwood". I have been employed with AstraZeneca UK Limited and

its predecessor companies for 30 years. I currently have responsibility for 6 people. I obtained a B.Sc. Chemistry (Hons 1st class) in 1976 from De Montfort University, and an M.Sc. in 1978 from the University of East Anglia. I have in excess of 20 years experience in the fields of medicinal chemistry and synthetic organic chemistry.

3. Attached are copies of laboratory note book pages of research chemists working under our direct supervision and control on this project. For the nine compounds exemplified in the application, five of the compounds were synthesized prior to September 21, 1998. The details are as follows:

Example Number	AR-C Number	Chemist Name	Lab Notebook Number	Page Numbers
1	130284	Andrew Bailey	2307	159-160
2	126583	Gemma Cansell	2345	25-26
3	126532	Simon Gulle	2335	47-48
4	130234	Barry Teobald	2295	178-183
5	130237	Barrie Martin	2274	157-156

4. In each case, attached is a copy of the cover showing the book number together with the relevant pages from the book. In several cases, the chemist lists the experiments carried out in a particular book at the front of the book. Where this is the case, such pages are attached to demonstrate that this represents the standard notebook. Where this was not available, the next page in the book is attached as evidence of routine standard use of the book.

5. The practice involves dating the top of the page at the start of the experimental with the date an experiment is started, demonstrating conception of the idea. Upon completing the experiment, the chemist signs and dates the end of the experimental write-up. The book is then countersigned and dated (note that for book 2274 page 158, there is a typographical error on the sign-off date - signed as "97" not "98").

We each declare that all statements herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that wilful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such wilful false statements may jeopardize the validity of the application or any patent issuing thereon.

Anthony H. Ingall

19 November 2001
Date

Brian Springthorpe

19 November 2001
Date

Attachments

2307

Andrew Bailey

2242 ← 2307 → 2407

previous book

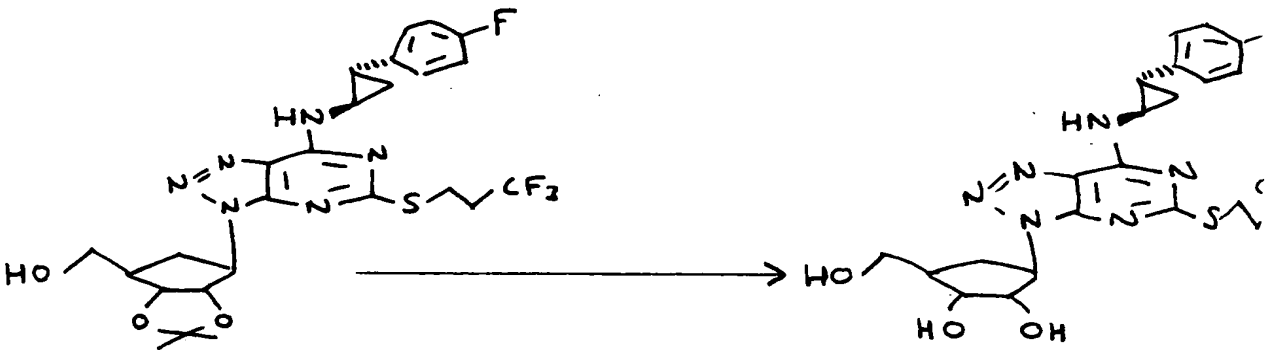
next book

1: 13/8/98 Prep^n of [1R-(1a,2a,3b,5b(1R*,2S*))]-3-[7-((2-(4-fluorophenyl)cyclopropyl)amino)-5-(3,3,3 trifluoropropylthio)-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl)-5-hydroxymethyl-cyclopentane-1,2-d

, A. Bailey

AB

AB



AB

$C_{25}H_{28}F_4N_6O_3S$ (568.5) $C_{22}H_{24}F_4N_6O_3S$ (528

AB

Method

AB

The S.M (1.4g) was dissolved in a mixture of trifluoroacetic acid (10ml) and water (2ml) and the soln left to stand for 50 mins at R.T

AB

TLC EtOAc/isohex (1/1)

SM.	O	
R.M	O	O O

AB

work up RM diluted with EtOAc and washed with xs aq. bicarb, organic layer dried, filtered and vacc'd down

AB

purification Flash column. 5 → 6% MeOH in $CHCl_3$

AB

Yield = 440 mg 'pure' + 250 mg 'less pure'

AB

AN° 298797 of the 440 mg of 'pure' foam

AB

HPLC 99.4%. major impurity 0.23%.

AB

MS APCI (+ve), M+H = 529

AB

NMR δ_{DMSO} 9.42 (d, 1H, NH), 7.27-7.22 (m, 2H, aroms), 7.14-7.08 (m, 2H, aroms), 5.01-4.95 (m, 2H, CH+OH), 4.73-4.70 (m, 2H, 2OH), 4.44-4.41 (m, 1H, CH), 3.87-3.84 (m, 1H, CH), 3.50-3.45 (m, 2H, CH_2), 3.26-3.13 (m, 3H, 3CH), 2.60-2.55 (m, 1H, CH), 2.28-2.20 (m, 2H, CH_2), 2.10-2.06 (m, 1H, CH), 1.90-1.80 (m, 1H, CH), 1.49-1.46 (m, 1H, CH), 1.33-1.30 (m, 1H, CH) missing H under solvent peak at 2.5? 5

AB

MA Theory is for 0.42 moles H_2O ie MWt = 536

Theory	C = 49.30	H = 4.67	N = 15.68	S = 5.98
found	48.91	4.38	15.62	5.92

AB

410 mg submitted as 130284XX

AB

AN° 298852 of the less pure 250 mg

AB

MS/NMR okay, HPLC 97.6%. major imp 0.48%.

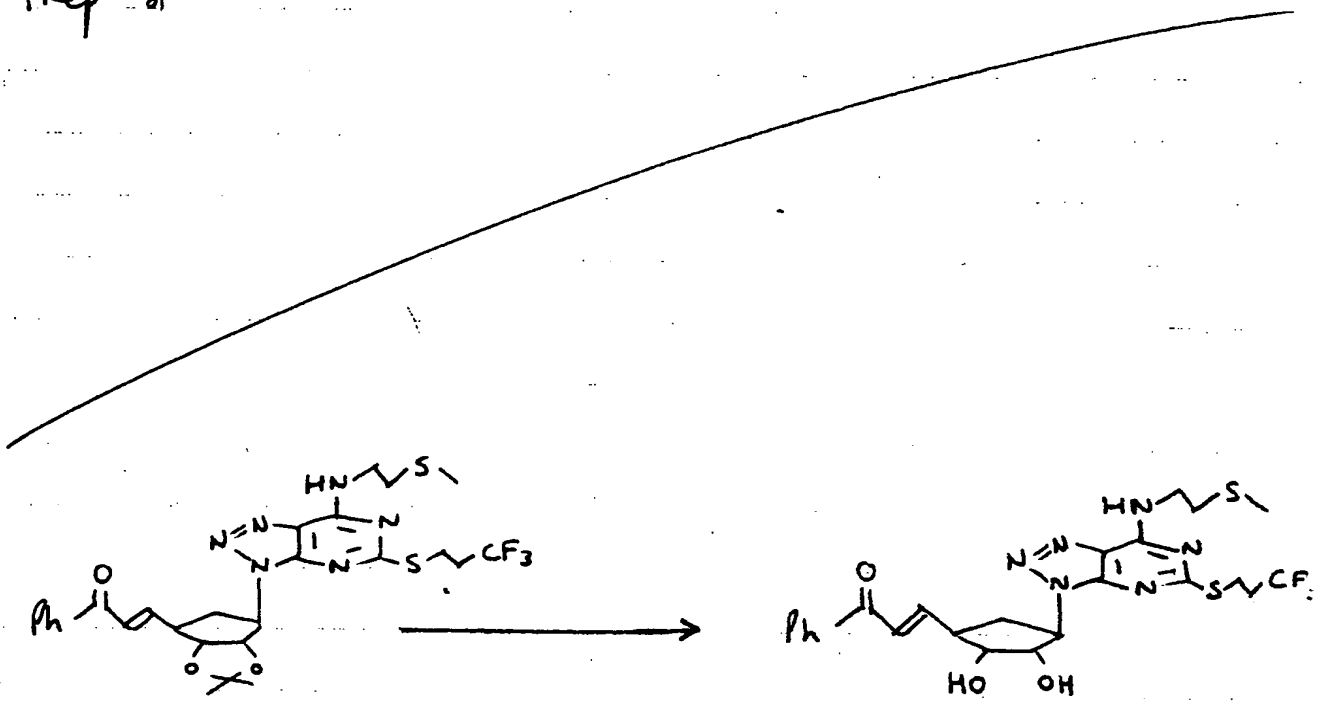
AB

180 mg as 130284XX Batch 2

COMPLETED

A. Bailey 22/9/98 READ AND UNDERSTOOD BY R. Jewell 02 OCT 1998

17/8/98 Prep^ of
A. Bailey



AD

$C_{27}H_{31}F_3N_6O_3S_2$ (608·7) $C_{24}H_{27}F_3N_6O_3S$ (568·6)

AB

Method

AB

The S.M (0·3g) was dissolved in a mixture of trifluoroacetic acid (10ml) and water (2ml) and the R.M was left to stand for 30 mins at R.T.

AB

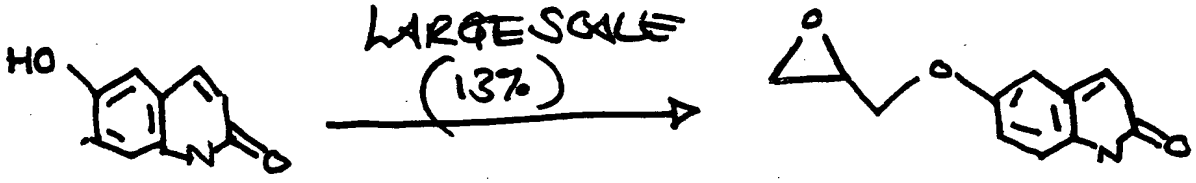
TLC 4% MeOH in $CHCl_3$

SM ·		0
RM ·	00	·

AB

work up RM partitioned between EtOAc and xs aq bicarb, the organic layer was dried, filtered and vacced down.

21



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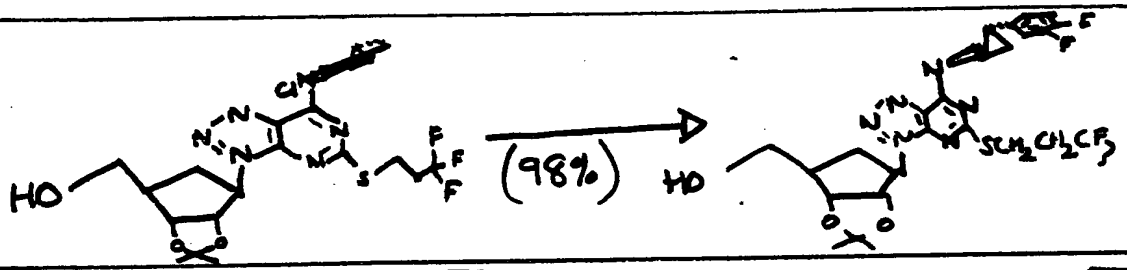

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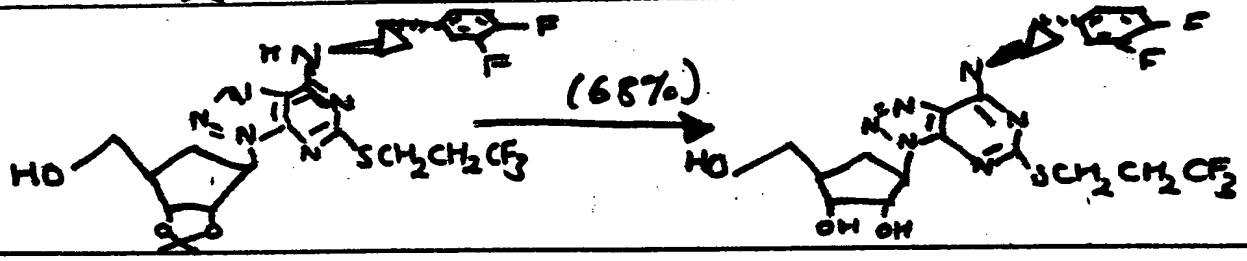

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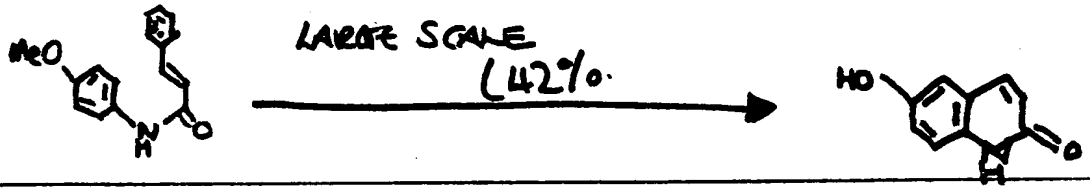
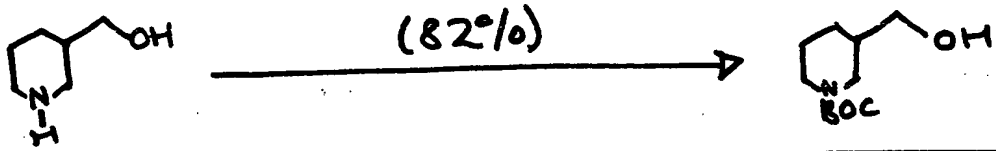
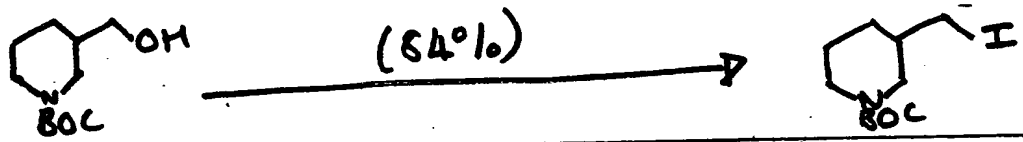


29



31



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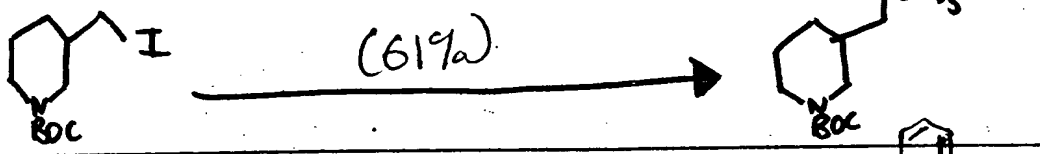
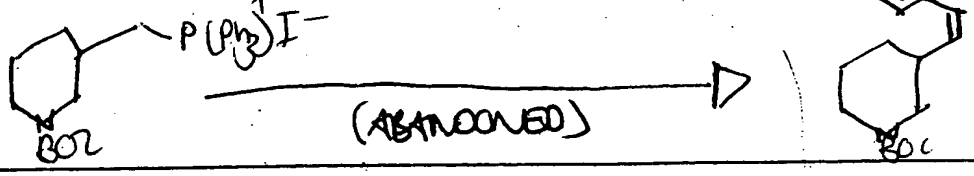
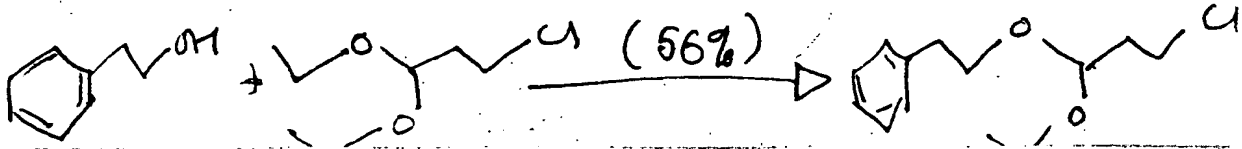


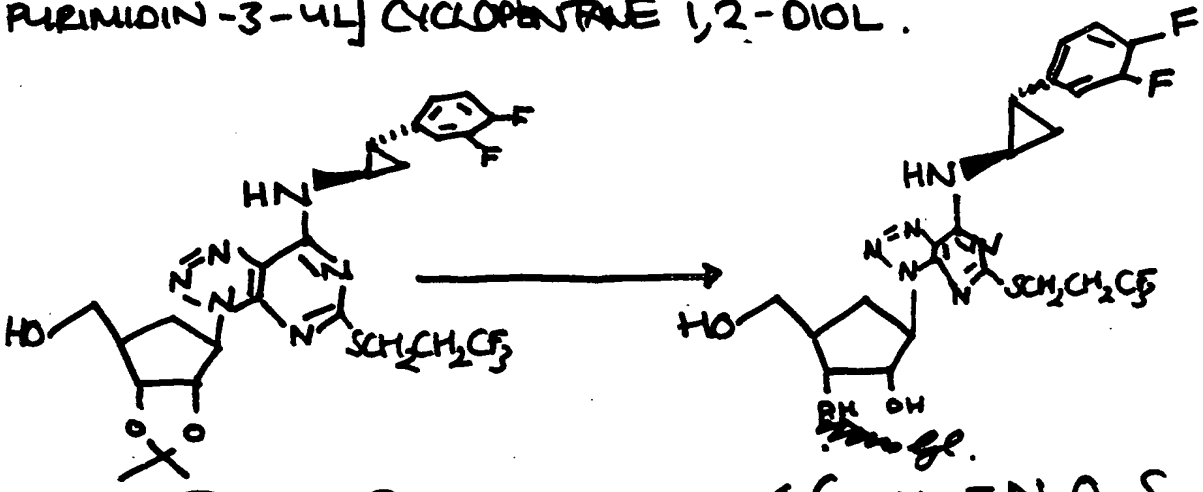
35



37



27/7/98. PREPARATION OF [3aR-(3aα,4α,6α(1R*,2S*),(6aα)]-6-(7-[[2-(3,4-DIFLUOROPHENYL)CYCLOPROPYL]AMINO]-5-(3,3,3-TRIFLUOROPROPYLTHIO)-3H-[1,2,3]-TRIAZOLO[4,5-d] PYRIMIDIN-3-YL] CYCLOPENTANE 1,2-DIOL.



$C_{25}H_{27}F_5N_6O_3S$ (586.584)

$C_{22}H_{23}F_5N_6O_3S$ (546.519)

METHOD The S.M (360mg, 0.614mmol) was dissolved in 10ml of methanol. The solution was treated with dilute aq. HCl (2ml, 3M). The RM was left to stand at RT for 2½ hours

TLC EtOAc/Isohexane (1:1)

SM.		O
MK.	O	O
RM.	O	(::

WORK UP R.M was partitioned between EtOAc + $NaHCO_3$. Organic layer was separated, dried and Vacced. down.

PURIFICATION. FLASH COLUMN, BIOTAGE, EthylAcetate (3) Isohexane (1). Removes S.M and final Product.

YIELD 229mg of White foam (68%).

~~ANS~~.

AN° APCI(+VE) M+H = 647.3 / (-VE) = 545 2.

MS 298022

NMR δDMSO D_6, 9.43 (O,1H,NH), 7.35–7.28 (M,2H,ARO) 7.02-7.14 (M,1H,ARO), 5.01 - 4.96 (M,2H), 4.72-4.69 (T,2H) 4.44 - 4.41 (Q,1H) 3.87 - 3.84, (Q,1H) 3.50-3.44 (M,2H) 3.25 - 3.12 (M,3H), 2.58 - 2.56 (M,1H), 2.28-2.21 (M,3H), 1.76-1.91 (M, 1H), 1.52-1.50 (M,1H), 1.39 - 1.37 (M, 1H), 1H MISSING, SUSPECTED UNDER SOLVENT.

10/9/98

HPLC 99.7%

COMPLETED
READ AND UNDERSTOOD BY J. McNally 18/9/98

ELEMENTAL Theory C=48.35% H=4.24% N=15.38% S=5.87% F=17.38%.
FOUND 49.38 4.71 15.26 5.71
(1% extra on hydrate)

IR

(cm-1)	(%T)
3288	96.03
1520	75.
1454	75.71
1435	76.17
1366	87.35
1322	87.14
1274	85.43
1240	72.47
1132	76.35
1087	73.28
1042	72.06
991	74.84
955	84.16
891	78.89
812	83.72
772	82.47
688	76.17
638	79.12
	73.92

120mgs entered as:-
135mgs

126583 XK

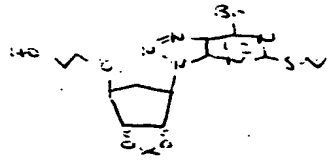
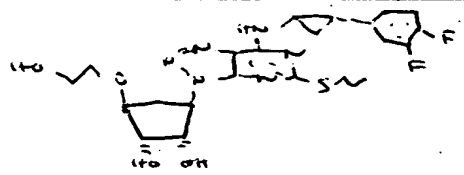
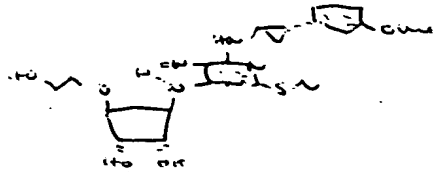
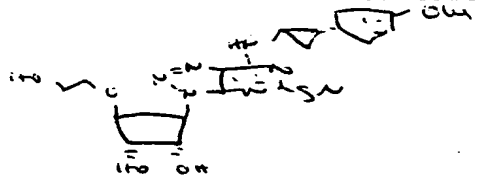
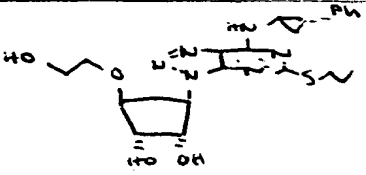
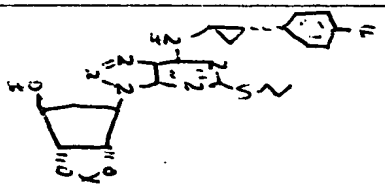
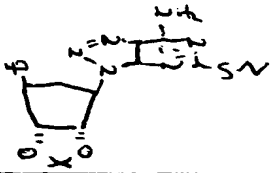
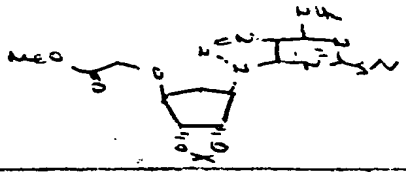
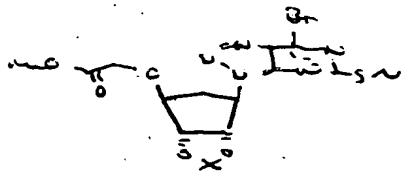
Simon D Guile

Medicinal Chemistry

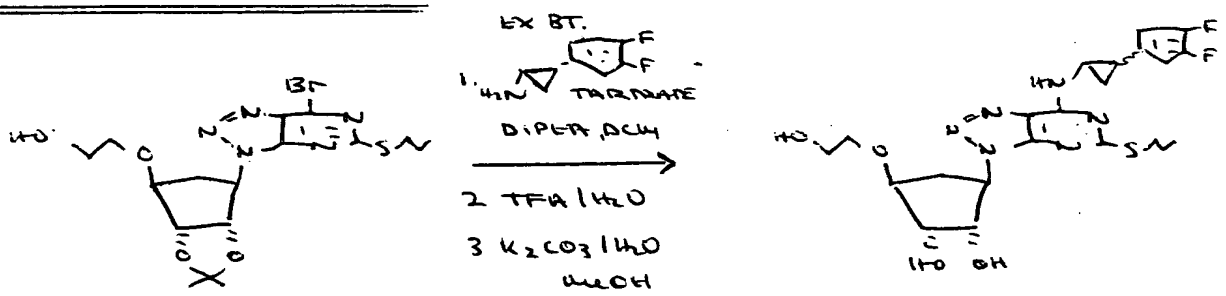
Astra Charnwood

Previous Book 2250

Next Book 2509

PLATE	PREPARATION OF...	YIELD	AR#
45.		42%	—
47.		48%	AR-C 126532XX
49.		73%	AR-C 126533XX
51.		53%	AR-C 126534XX
53.		31%	AR-C 120492XX BATCH 3
55.		82%	—
57.		100%	—
59.		38%	—
61.		42%	—

15/7/98 PREPARATION OF ~~[2-OH]~~ [1R-[1α,2β,3β(1R*,2S*),5β]]-3-[7-[(3,4-DIFLUOROPHENYL)CYCLOPROPYL]AMINO-5-(PROPYLTHIO)-3H-1,2,3-TRIAZOLO[4,5-d]PYRIMIDIN-3-YL]-5-[(2-HYDROXY)ETHOXY]CYCLOPENTANE-1,2-DIOL



(474.383)

2335/45A

(522.675)

$C_{23}H_{28}F_2N_6O_4S$

AMOUNTS

(474.383)	SUBSTRATE	75 mg,	0.16 mmol, 1eq
(319.26)	AMINE TARTRATE	66 mg,	0.21 mmol, 1.3eq
0.742 (129.25)	DIPEA	83 µl,	0.47 mmol, 3eq
	DCM	5 ml	

EXPERIMENTAL

A mixture of the above reagents was stirred at rt for 24 hrs. The reaction mixture was absorbed on to silica and purified (Biotage 1/1 EtOAc/Hex).

⇒ 2335/47A

AN 297523

LC/MS APCI+ 563 $(M+H)^+$ >99% PURE

The protected compound was treated with TFA/H2O (10 ml; 9:1) for 10 mins then concn in vacuo. The residue (mix of prod + TFA ester) was treated with K_2CO_3 (100 mg) in MeOH/H2O (10 ml; 1:1) for 1 hr.

This mixture was concn to remove MeOH. The remainder was partitioned between water (20 ml) and EtOAc (3×20 ml). The combined organic phase was dried ($MgSO_4$) and concn in vacuo then triturated with pentane to produce a solid

⇒ 2335/48A Purified RPHPLC ⇒ 2335/48B 40mg, 48%

AN 297547 (48A) / 297735 (48B)

LC/MS 98.4% MAJOR IMPURITY 1.6% APCI+ 523 ($M+H^+$)

IR

EA FOUND C 50.64% H 5.43% N 15.87% S 5.72%

REQUIRED C 51.10% H 5.59% N 15.55% S 5.93%

FOR $C_{23}H_{28}F_2N_6O_4S \cdot H_2O$ FW 540.59.

^1H NMR DMSO 0.79–1.00 (m, 3H), 1.20–1.75 (m, 4H), 1.96–2.30 (m, 2H), 2.58–2.70 (m, 1H), 2.80–3.20 (m, 3H), 3.43–3.58 (m, 4H), 3.73–3.80 (m, 1H), 3.90–3.96 (m, 1H), 4.50–4.61 (m, 2H), 4.96 (q, J = 9.0 Hz, 1H), 5.05 (d, J = 3.9 Hz, 1H), 5.11 (d, J = 6.3 Hz, 1H), 7.00–7.10 (m, 1H), 7.22–7.40 (m, 2H), 9.36 and 8.97 (m, 1H)

30 mg Submitted as ~~AR~~

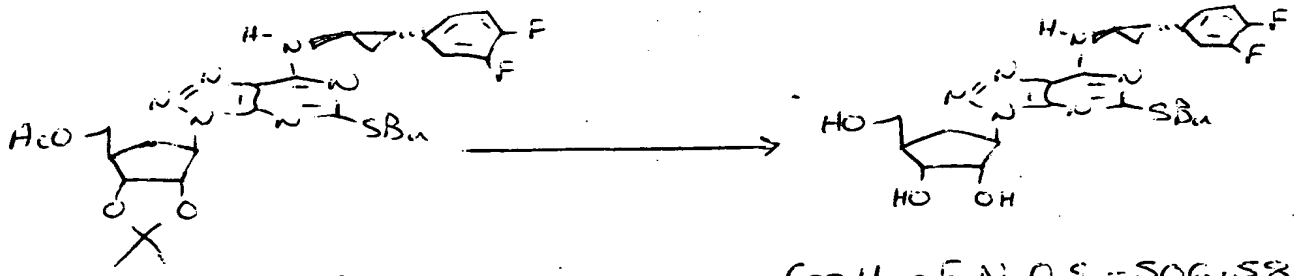
AR-C126532XX

COMPLETED 23/7/98 IAS Walters 13/11/98

READ AND UNDERSTOOD BY

2295

29-7-98 The Attempted Preparation of [1S-(1α, 2α, 3β, 5β (1S*, 2R*))]-3-[5-Butylthio-7-[[2-(3,4-difluoro-phenyl)cyclopropyl]amino]-3H-[1,2,3]-triazolo[4,5-d] pyrimidin-3-yl]-3-hydroxymethyl-cyclopentane-1,2-diol

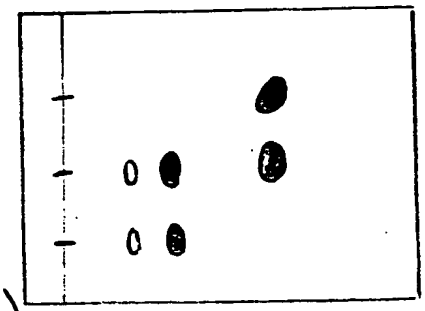


$C_{28}H_{34}F_2N_6O_4S = 588.68$ $C_{23}H_{28}F_2N_6O_3S = 506.58$

Protected nucleoside	0.226g	0.384mmol 1eqiv 2295/175/2
80% HCO_2H/H_2O	10ml	
10% K_2CO_3/H_2O	1ml	
MeOH	10ml	

A colourless solution of [3aR-(3aα, 4α, 6α(1R*, 2S*), 6aα)]-acetic acid, [[6-[5-butylthio-7-[[2-(3,4-difluoro-phenyl)cyclopropyl]amino]-3H-[1,2,3]triazolo[4,5-d]-pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]methyl]ester (0.226g, 0.384mmol) in 80% acetic acid/water (10ml) was heated in an oil bath at 80° for 1hour. Tlc indicated that some reaction had taken place:-

B.T.



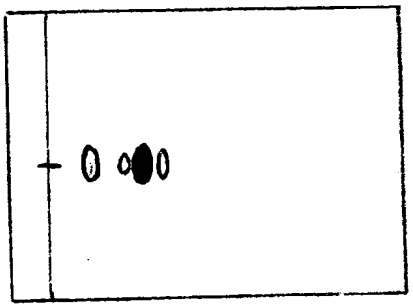
2295/175/2
Mixed Spot
Reaction Mixture
($NaHCO_3/H_2O$/EtOAc)

SiO_2
5% MeOH/CH_2Cl_2
U.V.

B. Teobald. 12-8-98

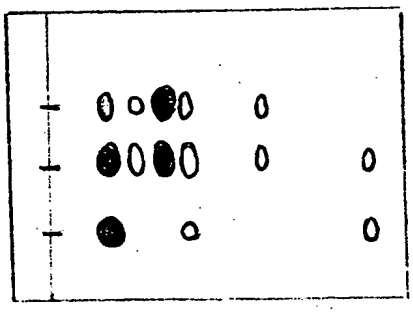
The reaction mixture was allowed to cool and was cautiously poured into saturated sodium bicarbonate solution (150ml). The resulting emulsion was extracted with ethyl acetate (3x 35ml). The combined organic phases were washed with saturated sodium bicarbonate solution (70ml), dried ($MgSO_4$) and concentrated in-vacuo to give a pale yellow gum (0.220g, 2295/178/1). Tlc indicated that 2295/178/1 was a mixture :-

B.T.



B.T. 2295/178/1 (0.220g) was dissolved in methanol (10ml) and to this ~~colourless~~ pale yellow solution was added a 10% aqueous solution of potassium carbonate (1ml). The resulting pale yellow solution was stirred at room temperature for 1/2 hour. Tlc indicated that some reaction had taken place :-

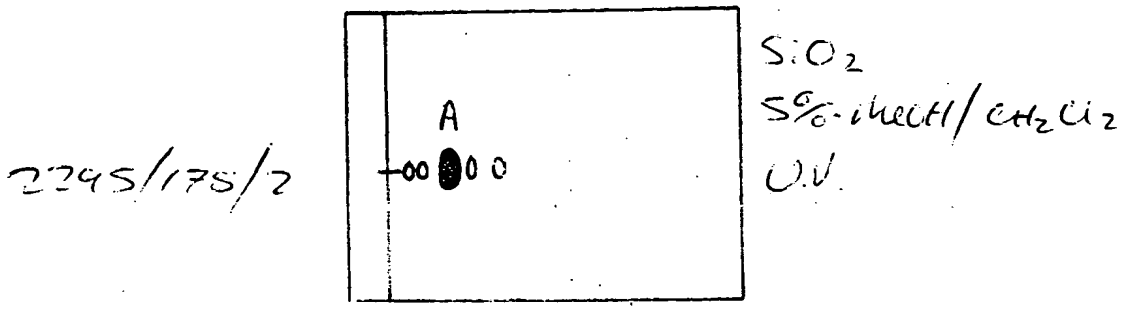
B.T.



The reaction mixture was neutralized to pH = 7

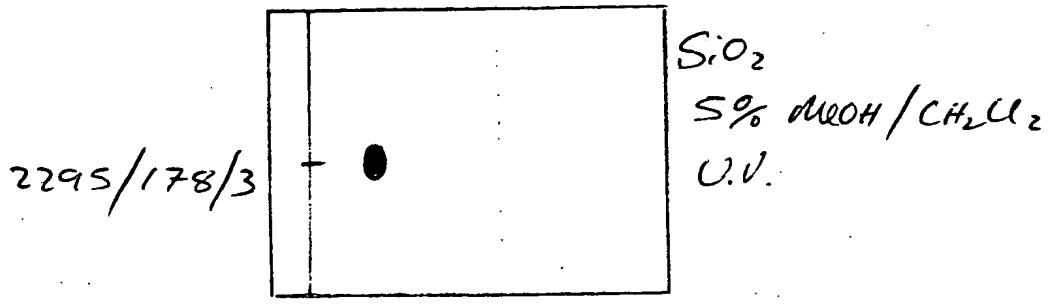
using a few drops of acetic acid and was then concentrated in-vacuo to give a sticky off-white residue (0.543g, 2295/178/2). Tlc indicated that 2295/178/2 was a mixture :-

B.T.



2295/178/2 (0.543g) was dissolved in a mixture of dichloromethane and methanol and was adsorbed onto flash silica (5ml, FISHER Matrex 60, 35-70μm) in-vacuo. The resulting free-flowing white powder was loaded onto a column of silica (54ml, as above) and eluted with 5% methanol in dichloromethane. Fractions containing essentially pure component 'A' were combined and concentrated in-vacuo to give a colourless residue which was dissolved in diethyl ether and re-concentrated to give a white foam (0.166g, 85%, 2295/178/3). Tlc indicated that 2295/178/3 was pure :-

B.T.



2295/178/3 (0.166g) was dissolved in a mixture of tetrahydrofuran and acetonitrile

B. Teobald. 12-8-98

to a concentration of approximately 20 mg/ml. The resulting solution was filtered and aliquot containing ~ 20 mg were purified by preparative HPLC on a Waters Novapak column eluted with 0·1% aqueous ammonium acetate and acetonitrile, isocratic mixture, 50% acetonitrile over 15 minutes, monitoring at 254 nm. Fractions containing the main peak were combined and concentrated in-vacuo to remove most of the acetonitrile from the mixture. The resulting sticky suspension was freeze dried to give a white fluffy solid (0·70 g, 2295/178/4).

AN298282 2295/178/4

NMR

^1H D_6-DMSO Shows the material to be the desired product, essentially pure:-

B.T.

δ_H 9·34 & 8·94 (Total 1H, 2 x bd, NH); 7·32 (2H, m, H-12 & H-15) 7·06 (1H, m, H-16); 4·99 (2H, m, H-1' & 1 x OH); 4·72 (2H, m, 2 x OH); 4·43 (1H, m, H-2'); 3·88 (1H, m, H-3'); 3·79 & 3·16 (Total 1H, 2 x m, H-8); 3·48 (2H, m, H-6'); 3·10 & 2·93 (Total 2H, 2 x m, H-17); 2·26 (1H, m, 1 x H-5') 2·11 (2H, m, H-4' & H-10); 1·84 (1H, m, 1 x H-5');

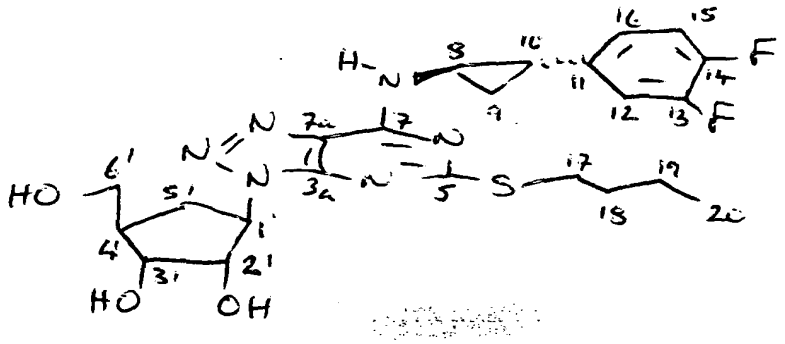
B.T. 1·65 & 1·46 (Total 2H, 2 x m, H-18); 1·55 (1H, m, 1 x H-9); 1·37 (1H, m, 1 x H-9); 1·24 (2H, m, H-19), 0·91 & 0·81 (Total 3H, 2 x t, 7Hz & 7·3Hz, H-20)

B.T.

^{13}C D_6-DMSO Shows the material to be the desired product, essentially pure:-

δ_C 169.1 (C-5); 153.9 (C-7); 149.4 (dd, 245 Hz & 12 Hz, C-13); 149.3 (C-3a); 147.8 (dd, 243 Hz & 13 Hz, C-14); 139.2 (C-11); 123.2 (C-7a); 122.8 (C-16); 117.0 (d, 17 Hz, C-15); 114.8 (d, 18 Hz, C-12); 74.9 (C-2'); 71.8 (C-3'); 63.0 (C-6'); 62.2 (C-1'); 45.4 (C-4'); 34.0 (C-8); 31.0 (C-17); 30.1 (C-18); 29.0 (C-5'); 24.0 (C-10); 21.2 (C-19); 15.0 (C-9); 13.5 (C-20)

B.T.



B.T.

IR. Okay:-

Wave Number (cm-1)	Threshold (%T)
2703	100.2
2361	99.36
2340	99.89
1609	84.73
1589	86.21
1520	85.94
1454	92.2
1430	93.59
1322	81.81
1275	87.42
1211	89.07
1115	89.71
1044	89.71
992	92.51
892	92.97
857	94.53
808	91.41
773	86.68
617	85.54
579	84.26

Teobald.

B.T.

HPLC Symmetry C8 0.1% NH_4OAc (aq) / CH_3CN 25-95% CH_3CN

RT (mins)	%
2.18	99.7

B. Teobald. 12-8-98

MS LC/APCI(+ve) 507 $(M+H)^{\oplus}$
507 (100%)

B.T.

m.p. No melting point as material is a freeze dried solid.

B.T.

Elem.

	%C	H	N	S
Found	53.41	5.47	16.00	6.26
	53.58	5.67	16.30	6.22

• $1/2 H_2O$ Requires
⇒ MW = 515.57

B.T.

78mg Submitted as AR-C130234XX
B. Teobald. 12-8-98

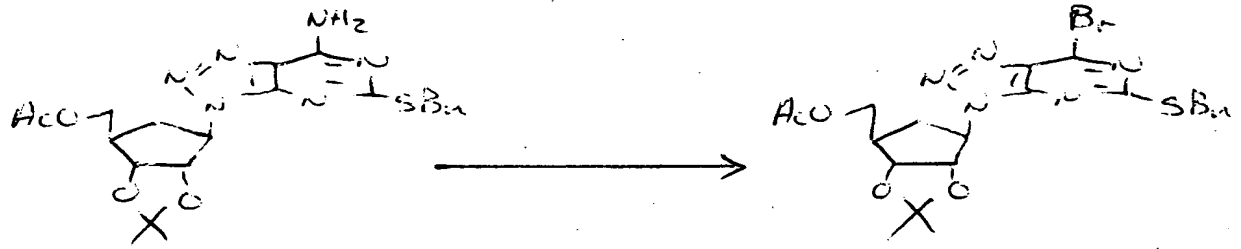
A

COMPLETED —
READ AND UNDERSTOOD BY S.C.K. 9-9-98

30-7-98 The Attempted Preparation of [3aR-(3ax, 4x, 6x, 6ax)]-Acetic acid, [[6-[7-bromo-5-butylthio-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]-tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]methyl] ester

Ref: 2295/172

B.T.

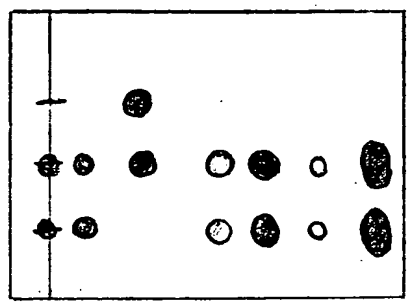


$C_{19}H_{28}N_6O_4S = 436.54$ $C_{19}H_{26}BrN_5O_4S = 500.42$

Protected nucleoside	2.13g	4.88 mmol	2295/164/2
Bromoform	23ml		
ONO	4.7ml		

B.T. A yellow solution of [3aR-(3ax, 4x, 6x, 6ax)]-acetic acid, [[6-[7-amino-5-butylthio-3H-[1,2,3]triazolo[4,5-d]pyrimidin-3-yl]tetrahydro-2,2-dimethyl-4H-cyclopenta-1,3-dioxol-4-yl]methyl] ester (2.13g, 4.88 mmol) in bromoform (23ml) and isoamyl-nitrite (4.7ml) was heated in an oil bath at 80° for 1/2 hour. Tlc of the resulting golden yellow solution indicated that the reaction was complete:-

B.T.

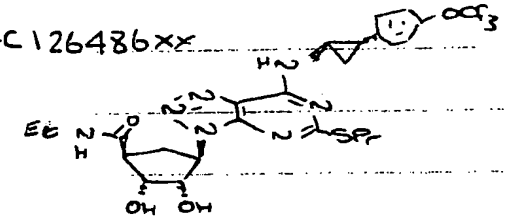


2295/164/2
Mixed Spot
Reaction Mixture

SiO_2
60% Et_2O/Isohexane
U.V.

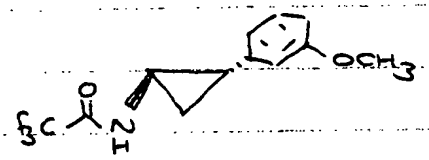
B. Teobald. 12-8-98

AR-C126486XX



58%

149.



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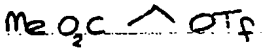
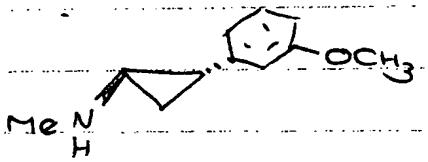
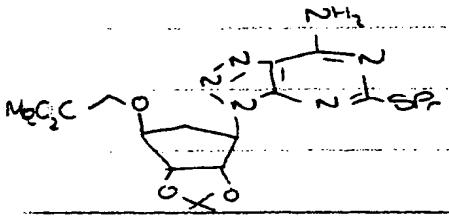


83%

151.



153.



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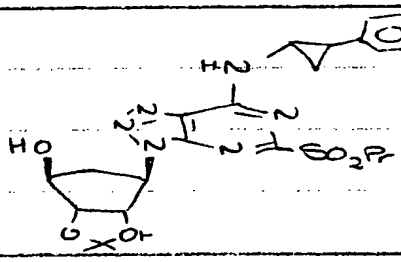

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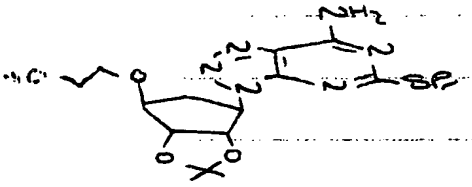

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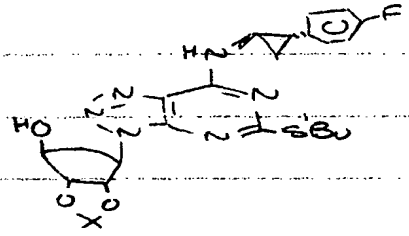
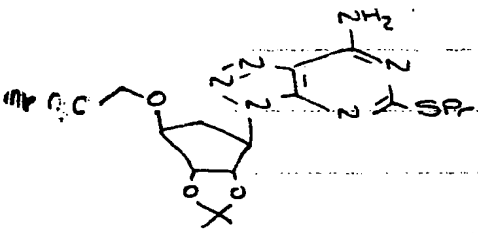
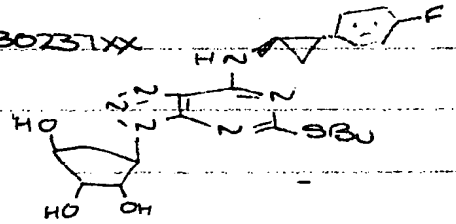


84

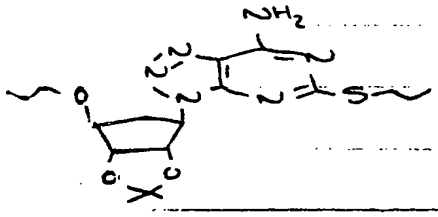


45%

157. AR-C130237XX

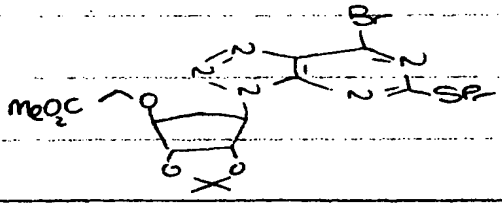


95%



74%

159.



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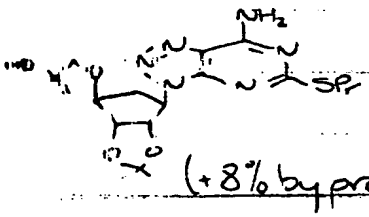
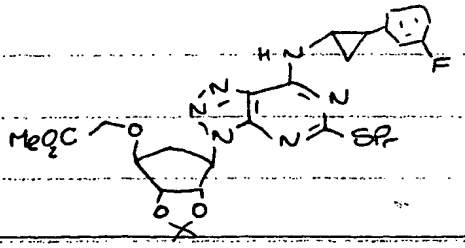


(+8% by product) 65%

161.

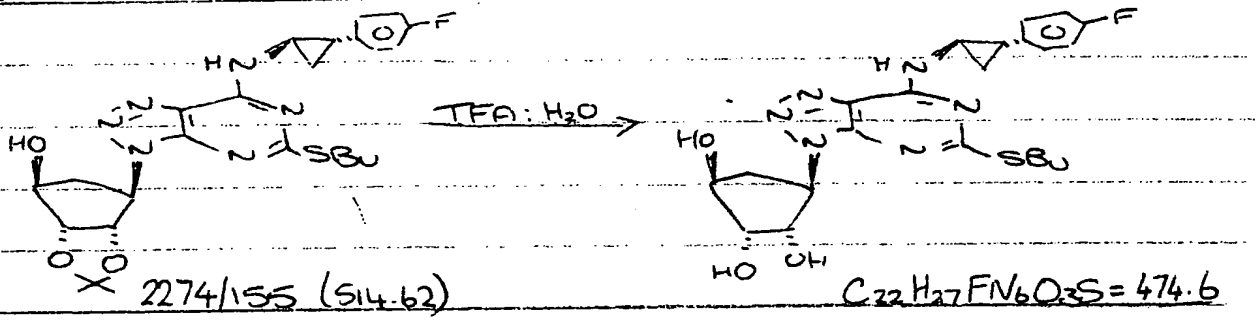


75%

AR-C 130237 XX

30-7-98

1S-[1α,2β,3β,4α(1S*,2R*)]-4-[7-(2-(4-Fluorophenyl)cyclopropylamino-5-propylthio-3H-1,2,3-triazolo[4,5-d]pyrimidin-3-yl]cyclopentane-1,2,3-triol.



2274/155 (514.62) $C_{22}H_{27}FN_6O_3S = 474.6$

2274/155 (690mg, 1.34mmol) was dissolved in water (10ml) and TFA (10ml), after stirring for 1hour reaction was complete by HPLC.

The reaction mixture was added dropwise to sat. $NaHCO_3$ (250ml) soln, and then extracted into ethylacetate (3×100ml). The organics were dried ($MgSO_4$), filtered and concentrated to dryness, the residue was then purified by RPHPLC to give a white solid (620mg, AN 298217)

Yield = 620mg (95%)

AN 298217

Infra-red: 1321, 1611, 1588, 1511, 1044, 1228, 818, 789, 1277, 1189, 1098, 834

HPLC: A7505AP.M RT = 2.14min, 99.55%

mass spec: APCI +ve M+H = 475.1 (100%)

Elem. anal $0.8H_2O = 489.01$	C	H	N	S
$C_{22}H_{27}FN_6O_3S$	53.99	5.85	17.18	6.54
Found	54.04	5.82	17.02	6.54

AN 298217

proton NMR (300 mH_3, d6-DMSO)

0.80 t, J = 7.5 H_3, 3H 1)

1.22 sex, J = 7.2 H_3, 2H 2)

1.30-1.35m 1H 7a)

1.41-1.53m 3H 7b) 3)

1.86-1.91m 1H 8)

2.11-2.15m 1H 18a)

2.51-2.59m 1H 18b)

2.80-3.00m 2H 4)

3.13-3.35m 1H 6)

3.77 bs 1H 16)

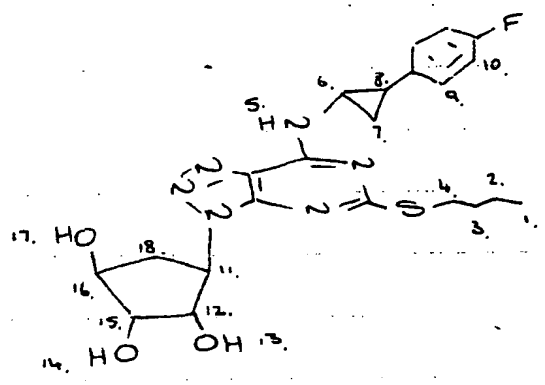
3.93 bs 1H 15)

4.63-4.67m 1H 12)

4.90-4.99m 1H 11)

7.11 t, J = 9.0 H_3, 2H, 9)

7.22-7.26m 2H 10)



melting point: 75-78°C.

590 mg submitted as AR-C130237xx

6-8-97